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TREATMENT in General Practice

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FIFTH EDITION, RESET

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MADE IN U. S. A.

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PHILADELPHIA

Dedicated to my wife

JANE SMITH BECKMAN

and our son

THOMAS HOWELL BECKMAN

PREFACE TO THE FIFTH EDITION

The prodigious upheaval in which the world is now involved has deeply affected the science and art of medicine. Great numbers of young men and women in the armed forces and of individuals of all ages in civilian life have been forced into unaccustomed types of existence. Unprecedented migrations have occurred. Larger numbers of people have been brought under medical observation than ever before in history. Many physicians are today in charge of wards and even entire hospitals filled with cases of a single disorder of which in times gone by they perhaps saw only a case or two a year. Many others are dealing *en masse* with serious diseases whose names were scarcely known to them before the Germans and the Japanese erupted. Nor is it only those on foreign service who are affected; for back at home the leaven is also at work and considerable changes have taken place in medical education and practice. Old concepts have fallen and new ones have arisen, and in some cases fallen too; laboratory research has been stimulated; facilities for large-scale clinical investigations have become available; fresh minds have been brought to bear on problems both new and old; and notable additions have been made to our knowledge and understanding.

I have attempted to keep abreast of these numerous developments, to evaluate them, and to present them in a form which would be immediately usable to the medical student and the practicing physician. The revision for this edition of the book, as for that of its predecessors, has been as completely unsparing as progress itself is ruthless. In bringing all of the subjects up to date many of them have of necessity been completely rewritten. In addition, the following entities are included for the first time: *Acute Infectious Lymphocytosis*, *Ainhum*, *Airsickness*, *Anaphylactic Shock*, *Atypical or Virus Pneumonia*, *Benzol Poisoning*, *Blast Syndrome*, *Boutonneuse Fever*, *Bullis Fever*, *Cardiogenic Shock*, *Cerebral Shock*, *Chemical Burns*, *Crush Syndrome*, *Dimorphic Anemia*, *Epidemic Influenza*, *Gas Gangrene*, *Human Serum Jaundice*, *Idiopathic Hypoprothrombinemia*, *Periodic Mastalgia*, *Phosphorus Poisoning*, *Primary Shock*, *Rh Factor Syndromes*, *Salmonella Food Poisoning*, *Secondary Shock*, *Shellfish Poisoning*, *Subclassical Deficiency States*, *Sulfonamide Sensitization*, *Surgical Shock*, *Thermogenic Anhidrosis*, *Toxoplasmosis*, *Urogenital Syndrome*.

It is a pleasure to acknowledge my indebtedness to Bernice Clodius for her assistance in maintaining the files of the literature, for typing the final manuscript, and for reading the proof with me. The publishers have been as always most cordially helpful.

HARRY BECKMAN

MILWAUKEE

PREFACE

The neglect of thorough and painstaking teaching of therapeutics in this country is not so often the subject of serious consideration in our medical councils as it well might be. With only a few notable exceptions, the medical schools seem content if there is presented within their halls, usually to Junior students who have had as yet practically no contact with the sick, a ridiculously inadequate course of lectures, the rest being left to the teachers in the departments of medicine, pediatrics, obstetrics, etc. And these latter seem to shift the responsibility largely onto the gods, not through any culpability upon their part, but simply because in their immersion in the task of acquainting the student with the prodigious methodology of modern diagnosis no time is left for an exhaustive consideration with him of the treatment of disease. Hence it is that the therapeutic credo of the average young practitioner today contains but two articles: one, that there are certain therapeutic principles that invariably hold and that they need to be varied only in detail in the handling of particular diseases; and, the other, that the art of treatment is one that "comes" if only one has mastered the art of diagnosis.

It is in an attempt to shake, however feebly, the false foundations of these beliefs that the present book has been written. In it each of the principal diseases of man, exclusive of those that by prescriptive right belong within the domain of the legitimate specialties, has had its own peculiar therapy described, as that therapy has been evolved out of the experience of physicians all over the world. The true authors of the book, then, are those men and women whose names appear in the Bibliography. Whenever possible I have presented their work in their own words, but often it has been necessary to abstract and to condense, and not infrequently to present a subject in a manner and perhaps even from a point of view that has apparently little in common with that held by those who reported the original trials and observations. Always, however, I have looked upon myself merely as an editor, and I hope that no more than editorial liberties have been taken in any portion of the book. Of course it has not been possible to keep my own opinion invariably in the background; hence I elected in the beginning to write in the first person so that there might be at no time any confusion as to whose work or views were being presented.

Very humbly I recognize that the rather lengthy presentations of controversies that are to be found here and there in the book will give much offense to all save those who, like myself, have been even more disturbed by the indolent type of pedagogy that seeks sanctuary in the shameful words: "Upon this point we can say very little as the authorities are at present in disagreement." Only as I have thought and taught through the years have I been able to write, a limitation which I suppose every author recognizes. As for the many other shortcomings of the book, I can only assure the reader that, no matter how grievous he finds them, they can in no wise affect him so deeply as they do me, for only I can know with what bright hopes the work was planned and begun several years ago.

HARRY BECKMAN

MILWAUKEE, WIS.

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INFECTIOUS DISEASES

ACUTE INFECTIOUS LYMPHOCYTOSIS

A few years ago Smith (1941) reported two types of lymphocytic reaction of the blood which he designated as acute and chronic infectious lymphocytosis. The acute cases, which were the less frequently seen, manifested a short but striking leukocytosis with only minimal symptoms and physical signs of a nondifferential character. The chronic type was said to follow infection of the upper respiratory tract and to be accompanied by low-grade fever, which persisted for weeks or months, and such symptoms as anorexia, pallor, fatigability, and abdominal pain usually referred to the region of the umbilicus. All the patients were children. Duncan (1943) reported a case corresponding to Smith's acute type but with pronounced abdominal signs and symptoms at the onset and evidences of possible involvement of the nervous system during the first week of the disease. As the result of more extensive experience, Smith (1944) enlarged upon his description of the acute form of the disease and stated that hyperleukocytosis, with a relative and absolute lymphocytosis due to an increase in normal small lymphocytes, constitutes the most important element in the diagnosis. Elevated blood levels are said to persist from three to five weeks, the normal lymphocytes in this disease contrasting sharply with the atypical and abnormal mononuclear elements in infectious mononucleosis and with the lymphoblasts in leukemia; the Paul-Bunnell test, which is usually positive in infectious mononucleosis, is uniformly negative here. Biopsy of the lymph nodes in 2 cases revealed degeneration of the lymph follicles and striking proliferation of the reticuloendothelium of the sinuses. Smith's report of 3 patients from one family and 1 hospital contact, together with Finucane and Philips' (1944) report of an epidemic of 20 cases in a children's ward, indicates that the disease is both infectious and contagious; the possible incubation period seems to be between twelve and twenty-one days. I include a description of acute infectious lymphocytosis because it seems to represent a heretofore unrecognized communicable disease.

THERAPY

There is nothing to describe.

AINHUM

Ainhum is a disease which attacks the toes, usually but one toe at a time. A furrow appears at the digitoplantar fold and slowly extends and encircles the toe until it is separated from the foot. There is usually no pain, but the patient is often greatly inconvenienced by the fact that the toe beyond the constriction becomes bulbous and in the late stages dangles in an everted position. The course of the disease is slow, self-amputation usually occurring only after a number of years. Ainhum occurs in the dark-skinned races in India, Africa, South America, and to some extent in the West Indies, and a

few indigenous cases in Negroes have been seen in both Europe and the United States.

The cause of ainhum is unknown, though it has been speculatively considered by some to originate as a fungus infection; Spencer (1942) felt that in his case it was probable that the condition was a sequel to the underlying hyperkeratosis from which the patient had suffered for many years.

THERAPY

At present the only effective treatment consists in amputation of the involved toe.

ANTHRAX

(Woolsorters' Disease, Malignant Pustule)

Anthrax is an acute infectious disease of animals, especially herbivora, caused by *Bacillus anthracis*. It is transmissible to man, in whom it appears either in the cutaneous, pulmonary or gastro-intestinal form. Workers in hide, hair, bristles, wool, horn, and bone are particularly susceptible, but it may be contracted by butchers, veterinarians, farm laborers, and others in contact with animals; Pinkerton (1939) reported a case contracted through pelting an infected mink. The disease is also occasionally contracted from an infected shaving brush. The incubation period is usually three to five days but may be as short as twelve hours or as long as two weeks. The pustule and edema of the cutaneous form are usually of a distinctive character, but there is often in the beginning considerable disproportion between these local changes and the amount of constitutional disturbance as evidenced by fever, rapid pulse and malaise. Consciousness to the end being characteristic, the appearance of delirium—indicating meningeal involvement—is always an ill omen. The symptoms of the pulmonary and gastro-intestinal forms are not distinctive of the disease and thus the correct diagnosis is often made very late. There are usually about 100 cases of anthrax in man in the United States annually; the mortality rate was formerly very high but the newer types of therapy have brought it down in recent years to about 6 per cent.

Anthrax was described by Hippocrates (460–370 B.C.) in one of the books of Epidemic Diseases thought to have been the authentic work of the Coan master, and it appears to have been well known during the period (732–1096 A.D.) of Arabian and Jewish ascendency in medicine; but it is of interest to note that Galen (131–201 A.D.) had mistaken Hippocrates' description for that of erysipelas. The strange periodic malady of the middle ages, *malum malannum*, may have been anthrax, which is known with certainty to have been epidemic in the early seventeenth century. I believe the first complete treatise on the disease was that of Chabert, in 1780. Davaine discovered the organism in 1850, Koch demonstrated his cultures in 1876, Pasteur produced a preventive vaccine in 1880, and Sclavo, in 1895, offered the first of the serums which have since been widely used in therapy.

THERAPY

Local Treatment.—Other than the application of warm boric acid compresses, or of merely sterile gauze to collect the secretions, and the simple

incision of an abscess if it forms, it is nowadays considered that nothing should be done locally except to put the part at rest. Koschucharoff (1938) considered both incision and excision contraindicated on the basis of much experience with anthrax in Bulgaria; he stated that thermocautery might arrest the process if employed in the very early superficial stage but he also felt that there were many reasons operating against its routine employment. Most authorities agree that excision should not be done because of the difficulty of accurately defining the area to be excised and especially for the reason that general dissemination of the malady may be hastened by the manipulations. Enrich, discussing his treatment of 340 cases in the badly infected Bradford district in England, said that the results have been much better since the abandonment of excision in all cases except those in which the pustule is very small and on a site notoriously apt to favor rapid extension, such as the neck; but he insisted that a limb should be fixed by splints and pillows or the head held in position by a towel carried across the forehead and fixed beneath sand-bags. Lucchesi and Gildersleeve (1941), in the United States, followed a strictly "hands off" policy in their treatment of 67 patients without a fatality; so too did Gold (1942), who lost only one of his 60 patients, the fatal case having been inadequately treated systemically.

Antianthrax Serum.—The serum made by immunizing horses against virulent anthrax organisms has greatly reduced mortality throughout the world. It is given intravenously, the amount varying somewhat with the location of the lesion and the apparent virulence of the organism, but Gold (1942) stated that from 200 to 500 cc. should be given as an initial dose and that this should be repeated every twelve to twenty-four hours until edema is checked. Some observers have felt that the presence of adenopathy is an indication for the continuance of serum treatment, but Gold found that lymphoid enlargement may persist for days and weeks after the lesion has healed and the patient is on the road to complete recovery and that it gradually disappears without any therapy; control of the edema he therefore held to be the most reliable yardstick in determining whether sufficient serum has been administered in a given case.

In addition to the systemic use of antiserum, Regan advised a number of years ago that the serum also be used locally, by which was meant the injection of 2 to 3 cc. at three or four equidistant points so as to circumscribe the lesion, the needle being inserted from 1 to 1½ inches subcutaneously in the red indurated border just beyond the blanched zone. It is not generally agreed that the local injections are of value, and Gold was of the opinion that in the only one of his cases in which he used them they only served to spread the infection by the mechanical separation of the tissues which they effected.

Sulfonamides.—Gold (1942), reviewing his experience in the treatment of 60 cases of anthrax, stated that he felt the sulfonamide compounds to be a reliable and safe substitute for serum and that they should be given preference in the treatment of anthrax. His average period of hospitalization was 15.3 days in serum-treated cases and only 8.5 days in sulfonamide-treated cases. The difference in the number of work days lost was even more striking; total disability in the serum-treated cases was 37.5 days while in the sulfonamide-treated (sulfapyridine, sulfathiazole or sulfadiazine) it was 15.4 days. In addition, the sulfonamide-treated patients could be kept at home and did not experience the unpleasant reactions associated with serum therapy.

Neoarsphenamine.—The drugs of this group have long been employed in

South Africa, but only in recent years has their use begun in other parts of the world. Gilbert (1936) reported a series of 13 cases, 11 of the patients recovering when treated by neoarsphenamine alone. Only one intravenous injection of 0.6 Gm. was usually given, but if the edema persisted after twenty-four hours it was repeated. In all cases in which patients recovered the edema was relieved in thirty-six hours and had disappeared in four days; the patients were ambulatory on the sixth day. Enrich (1933) was also impressed by the value of the arsenicals, but he gave his two doses with an interval of one day between and usually combined the use of antianthrax serum with this newer treatment method. Lucchesi and Gildersleeve (1941), summarizing their experience in 67 cases, felt neoarsphenamine to be the agent of choice unless the patient is afflicted with the internal type of anthrax, or the blood stream has been invaded, or the lesion is on the face or neck; in such instances they preferred to use serum. Gold (1942) wrote that neoarsphenamine did not prove to be of much value when given in addition to serum in a small number of his cases. In Bulgaria, where from 800 to 1100 cases of anthrax occur annually, Koschucharoff wrote, just prior to the outbreak of War II, that serum is used almost exclusively and neoarsphenamine employed only occasionally.

Penicillin.—Up to the time of writing in the early spring of 1945, the only report I have seen of the use of this agent in human anthrax was that of Murphy *et al.* (1944), who obtained excellent results with the systemic employment of penicillin in 3 cases. In each instance the inflammatory reaction about the lesion showed prompt regression and the lesion itself underwent rapid involution. It was the feeling of these observers that a total of 200,000 to 400,000 units, given at the rate of 100,000 units per twenty-four hours, would likely prove satisfactory dosage in the average adult case of uncomplicated cutaneous anthrax; it was felt that in cases of visceral anthrax or severe cutaneous anthrax with bacteremia larger doses should undoubtedly be employed, probably preferably by intravenous drip, and that perhaps serum should be given in addition.

ASIATIC CHOLERA

There are five major infectious diseases whose entire handling has been taken over quite properly by public health authorities or other specialists of great experience. These five are Asiatic cholera, leprosy, plague, trypanosomiasis and yellow fever; and since they do not nowadays raise problems in treatment for the general practitioner, I shall no longer allot space to a consideration of them in this book.

BLACKWATER FEVER

This syndrome, occurring only in malarious individuals, is characterized by sudden onset with a rigor of chill and high fever, vomiting, jaundice, oliguria and finally anuria, usually severe upper abdominal and loin pain, enlarged

and tender spleen, hemoglobinemia, hemoglobinuria, methemoglobinuria, "methaemalbumin" in severe cases (Fairley and Bromfield, 1939), albuminuria, rapidly progressive anemia, and a high death rate. There have been many speculations with regard to the causation of blackwater fever—for example, that it is a plasmodial infection complicated by some other parasite, such as Bartonella, or by an unknown virus; or that malaria with a tendency to blackwater has a different etiology from the ordinary form of the disease and may be caused by a specific plasmodium such as the *Plasmodium tenue* Stephens; or that several anophelines may be grouped into the single species *Anopheles funestus*, which is capable of modifying the malarial parasites so as to make them more apt to provoke blackwater. However, everything revealed in most of the careful studies of the occurrence of blackwater fever—such as the painstaking work of Whitmore in the West Indies and Central America, and of many others in Africa, India, and elsewhere—supports the belief that blackwater fever is a bizarre manifestation of *P. falciparum* infection. Witness the fact that Foy *et al.* (1942) injected 106 lunatics with the blood from 58 patients with blackwater fever; some of these subjects developed malaria but in not a single case did blackwater fever occur though the observation extended for a period of nine to eighteen months. But the distribution of blackwater fever is not entirely the same as that of falciparum malaria, for there are regions thoroughly saturated with the latter in which blackwater is not seen. Where prevalent it is usually the newcomers—and not always only white newcomers, as recently thoroughly substantiated by Burkwall (1943)—who are attacked; returning sojourners from malarious lands sometimes come down with it also even though they may not previously have had a typical malarial attack. The direct cause of the hemolysis has not yet been established, but the studies of Maegraith *et al.* (1943) produced interesting evidence of the ability of human tissues to lyse erythrocytes and the presence in serum of a factor which inhibits this lysis, the titer of the latter factor being reduced in blackwater fever; upon the other hand, the study of Foy and Kondi (1943) pointed toward the production in blackwater fever of a powerful hemolytic lysolecithin in the spleen.

THERAPY

Combating Anuria.—The oliguria, anuria and azotemia that occur in blackwater fever have been attributed to blockage of the renal tubules with the precipitated products of hemoglobin, and indeed study of kidney sections does reveal microscopically that the tubules are blocked, but we are still very far from an understanding of why this blockage occurs. Whether the liberation of hemoglobin into the blood stream is in itself a harmful thing cannot be said to have been decided as yet for there are experimental evidences on both sides of the question. As the result of an exhaustive review of the subject, Foy *et al.* (1943) concluded that the kidney changes result from extrarenal factors such as diminished blood volume, dehydration, and reduced circulation and glomerular filtration. Maegraith (1944) stated the belief that there occurs in blackwater fever a shock-like state of peripheral vascular atony and that the anuria may result in part from depression of glomerular filtration. The administration of fluids to the patient is certainly rational, but since vomiting usually precludes the use of the oral route, frequent small retention enemas of normal saline, or the introduction of saline by proctoclysis or by intravenous infusion, must be resorted to; the addition of 5 to 10 per cent of dextrose will aid in

sustaining the patient and combating acidosis. There is no evidence that oliguria and anuria occur more frequently in patients with acid urine than with alkaline; in fact, Foy and Kondi (1941) showed that anuria develops frequently in patients who have had only a small amount of hemolysis and passed alkaline urine and that it may fail to develop in patients in whom there has occurred considerable hemolysis and who have consistently passed acid urine. Nevertheless, the use of alkalis has dominated the treatment of blackwater fever for a good many years. Smith and Evans (1943) went so far as to advocate the intravenous administration two or three times daily of 20 cc. of 2 molar or 3 molar solutions of sodium lactate, despite the fact that these solutions cause thrombosis of the veins. They felt that their preliminary experimentation had shown that the fragility of red blood corpuscles is increased at low *p*H levels and decreased at high levels and that therefore the pushing of alkalis was rationalized on the basis of its prevention of intravascular hemolysis, but Dacie and Murgatroyd (1943) trenchantly remarked that the assumption of inhibition of hemolysis in blackwater fever as a result of the small changes in erythrocyte fragility produced by alkalosis is not warranted in the present state of our knowledge. Maegraith and Havard (1944) expressed the strong conviction that intensive alkali therapy is both ineffective and dangerous. Tomb (1942) convinced himself, and doubtless many others will be in agreement with him, that the kidney changes result from the diminished oxygen-carrying capacity of the blood, *i.e.*, that the kidneys fail to function as a result of anoxia. But this conception is not very practically helpful since the alleged anoxia is the result of hemolysis and we do not know what causes the hemolysis or how to check it.

The application of hot fomentations to the kidney region is said to be sometimes helpful in anuria and they are often analgesic as well.

Combating Anemia.—Smith and Evans (1943) said it has been calculated that a man may lose the equivalent of 4 to 6 pints of blood by intravascular hemolysis in thirty-six hours in blackwater fever. Red cells transfused to the patient are destroyed just as readily as the patient's own cells, indicating that there is some circulating hemolysin that destroys all red cells coming into contact with it irrespective of their origin. However, Blackie (1937), who gave the subject careful study over a period of five years in Southern Rhodesia, concluded that transfusion is an important life-saving measure if instituted early and repeated until there is evidence of active erythropoiesis; he believed transfusions to be contraindicated in toxic anuric cases. Smith and Evans (1943) gave up the use of transfusions in the first two days because of the frequency of severe reactions, and they stated that when giving a transfusion in blackwater fever it is probably best to start by giving only 20 drops in the first ten minutes, after which the transfusion may be proceeded with more quickly. Loutit (1943) said that in two cases he had good results from repeated transfusions with concentrated red cell suspensions without reaction.

In the after-treatment of the severe anemia the use of both iron and liver preparations is rational.

Nursing Care.—All agree that because of the rapidly developing and severe anemia there quickly arises great danger of circulatory failure of the type for which we unfortunately have no satisfactory remedial agents. The best weapon is prevention, which takes the form not only of having the patient in bed but keeping him quietly there by allaying his apprehension and restlessness with sedatives (see Insomnia); indeed, Burkitt (1943) claimed that the intra-

muscular or intravenous administration of $7\frac{1}{2}$ to 15 grains (0.5–1.0 Gm.) of phenobarbital sodium cures blackwater fever at once, which is very interesting if true.

Antivenene.—Singh and Singh (1944) reported good results from the use of snake venom antiserum in 36 cases; the administration of 20 cc. of the concentrated serum intravenously at once and the subsequent administration of 10 cc. every four hours for the next seventy-two to ninety-six hours were said to have prevented the occurrence of a second attack of hemolysis in their series.

Antimalarial Drugs.—There is considerable evidence, but none of a very scientific nature, that the taking of large amounts of quinine in the treatment of repeated attacks of malaria may be the factor that precipitates blackwater fever. At any rate it is certainly the consensus that the administration of quinine during the course of the attack is in most instances probably unwise. This is not, however, a matter of very great importance for two reasons: (*a*) the organisms usually disappear quickly from the bloodstream when the blackwater attack begins and hence there is not a pressing need for the use of an antimalarial drug during the first few days, and (*b*) atabrine (mepacrine, quinacrine) has apparently caused this syndrome in only a very few instances and therefore may be much more safely employed than quinine if it is necessary to use a drug during the acute period. A week to ten days after hemolysis has ceased, a course of atabrine (see Malaria) should be given to prevent a malarial relapse; Murgatroyd (1943) said that if quinine has to be used it should be given in a beginning dose of $\frac{1}{2}$ grain (30 mg.) three times daily and gradually increased up to 10 grains (0.6 Gm.). Fairley and Murgatroyd (1940) reported a case in which the capacity of quinine to produce blackwater fever appeared to be definitely related to persisting malarial infection, since after the apparent cure of the malaria quinine administration entirely failed to induce hemoglobinuria.

BRUCELLOSIS

(*Malta Fever, Mediterranean Fever, Undulant Fever*)

Brucellosis is an infectious disease caused by *Brucella melitensis*, *B. abortus*, and *B. suis*, the clinical manifestations being probably identical no matter which of these organisms is the infecting agent. *B. melitensis* is harbored by goats, apparently without being harmful to these animals, and is contracted by the human being through direct contact with the animal or through ingestion of its milk. The disease is endemic and epidemic in the Mediterranean littoral and elsewhere in the world where raw milk from infected goats is consumed. Where prevalent, it is a difficult disease to stamp out for the reason that the goat is a profitable animal in these regions and the sterilization of its milk renders it decidedly objectionable in taste. Besides, the goatherders in the rural districts refuse to believe that such a disease exists, perhaps because of their own immunity owing to a gradual vaccination.

Owing to the increasing prevalence of the disease in the United States and other countries where goat's milk as the carrier could be practically ruled out, search for some other organism capable of causing the disease was rewarded

by the discovery that *B. abortus* and *B. suis*, the organisms responsible for the infectious abortion of cattle, sheep and hogs, were also the etiologic agents in human brucellosis in many parts of the world. The disease, as contracted through ingestion of insufficiently pasteurized cow's milk, may of course appear endemically or in small epidemics; there are also many contact cases in farmers, butchers, sausage makers and veterinarians; work with this organism in the laboratory is very dangerous. Transmission from man to man has not been demonstrated. It is generally considered that one attack of the disease confers lasting immunity, and immunization of those frequently exposed doubtless often takes place without the development of a recognizable attack.

The symptoms closely resemble those of typhoid fever with influenza engrafted upon it, *i.e.*, there are more respiratory, myalgic and neuralgic symptoms than would be expected in typhoid; but tularemia, malaria, and indeed a number of other acute infectious diseases need to be ruled out, for brucellosis is inclined to be protean in its manifestations. Rheumatic symptoms, orchitis and epididymitis are of frequent occurrence; middle ear disease, and pharyngeal and laryngeal complications resembling those of tuberculosis and syphilis, are seen; lymph gland involvement with a histologic picture like that in Hodgkin's disease; spondylitis, endocarditis, meningitis, meningomyelitis, encephalitis, osteomyelitis, intermittent hydrarthrosis, pleurisy with effusion, cholecystitis and focalized hepatitis, hematopoietic damage, specific bronchopneumonic consolidation, and numerous other symptoms or complications have been reported. In short, in many instances the clinical diagnosis of acute brucellosis is made with extreme difficulty, and now that the existence of a subclinical, chronic form of the disease—taken out of the grab-bag known as "neurasthenia"—is being increasingly recognized, this disease has come to be one of major importance indeed. The usual incubation period is two weeks in the Mediterranean cases but it varies from slightly less than one week to several months; here in the United States it is thought to be several weeks in most instances. The course, even of the milder among the cases that are positively identified, is very protracted; mortality is in general fairly low (3 per cent in the United States, according to Huddleson *et al.*, 1939, and only about 1 per cent in the more recent opinion of Carpenter, 1943), but occasionally the attack may be of a quite malignant nature.

According to Calder *et al.* (1939) the most striking feature of the blood picture in their 271 patients was active lymphocytosis with an unusually high proportion of immature lymphocytes in the peripheral blood; coagulation time was also prolonged and clot retraction was imperfect. I think it is now the consensus that none of the three tests—the intracutaneous, agglutination and opsonocytophagic—is of specific diagnostic value since any one of them may be positive in asymptomatic cases and all may be negative in cases proved by culture of the organism from the blood. Harris (1943) evaluated these tests as follows: if the intracutaneous and agglutination tests and the culture are all negative, we do not know whether or not the patient has ever had brucellosis and therefore the opsonocytophagic test, which merely indicates the degree of opsonic activity of the blood toward Brucella, has no interpretable diagnostic significance; if the intracutaneous test is positive we know that the patient has an old or a recent infection, of undetermined activity; if the positive intracutaneous test is accompanied by a low opsonocytophagic test it is presumptive evidence that the patient has not recovered from the infection, but if it is accompanied by a high opsonocytophagic test the patient may be presumed

to have recovered from the infection; positive culture from blood, urine, feces, sputum, bile, synovial fluid, or other exudate, discharge, or tissue alone is definitive, but there is a reasonable expectancy of recovering the organism only in the presence of acute infection.

THERAPY

The symptomatic treatment is such as would ordinarily be instituted in typhoid, influenza, acute arthritis, etc. In describing the handling of a small milk-borne epidemic of the disease, Borts *et al.* (1943) stressed the fact that bed rest during the course of the acute illness and for ten days to two weeks after the temperature has returned to normal is probably the best assurance against extended illness. In addition to bed rest and symptomatic treatment a considerable number of other things is usually tried, and I have attempted to outline below the method of employing the chief of these measures. But it seems apparent that still today as in 1936, when Carpenter and Boak thoroughly reviewed the subject, we have no specific agent which can be counted upon to influence favorably all the cases in which it is used. Witness the report of Spink *et al.* (1941): of 12 patients receiving only symptomatic therapy, 9 improved; of 11 receiving measures thought to be more or less specific, 7 improved.

Vaccine.—It would seem that whatever is attainable with vaccine therapy is attributable to the general foreign protein reaction and is therefore obtained as easily with typhoid as with brucella vaccine; the latter is no longer Council-accepted. Castaneda and Cardenas (1941), in Mexico, experimented with a vaccine prepared according to a new method but their results were not striking. It does not seem to me that the results obtained by Calder (1939) with a vaccine prepared by Foshay were very remarkable either; in some cases he thought intravenous administration of nicotinic acid was additionally helpful.

Hyperthermia.—Prickman *et al.* (1938), at the Mayo Clinic, treated a small group of patients by inducing fever in the Kettering hypertherm; they felt their best results were obtained in acute and subacute cases; in a more recent report (Phalen *et al.*, 1942) the satisfactory treatment of 3 cases of brucellosis spondylitis was described. I understand this type of therapy is being employed currently with a modicum of success throughout the country, but Levitt (1943) wrote that it had been employed with indifferent results at the Cook County Hospital.

Brucellin.—Huddleson has been the chief advocate of a filtrate of a broth culture of brucella. If there is no marked systemic reaction in twenty-four hours to the preliminary intradermal injection of 0.1 cc. of this material (brucellin), he gives 0.2 cc. intradermally and 0.8 cc. intramuscularly in the afternoon or evening; this induces systemic reaction and he likes to induce such reactions three or four times at intervals of three days. Huddleson (1939) reported 500 cases treated by himself and a number of widely scattered physicians and considered the results favorable, but I am wondering if time will show this treatment to have more value than any other type of foreign protein therapy. Borts *et al.* (1943) used brucellin in all 77 of the patients involved in the epidemic reported by them, giving the injections at intervals of three to five days until 3 doses had been given after the febrile reaction had ceased to be produced. The average number of injections was 15, which means that their patients were stuck 15 times at intervals of three to five days with the avowed purpose in all save the last 3 doses in each instance of causing a febrile

reaction—to my mind the results would have to be extremely good to justify that sort of treatment, but nothing very specific is said about the results in Borts' report.

Whole Blood Transfusion.—Quelvi and Nelson (1932) were very favorably impressed by their results with one or two transfusions by the usual method in 9 of their 10 cases, but since their report a good many transfusions have been given without setting any therapeutic rivers afire.

Immunotransfusion.—Creswell and Wallace (1936) reported favorably (see Index for method), but I have not seen a subsequent report of the use of this type of treatment.

Human "Immune" and Convalescent Serum.—Poston and Smith (1936) injected human immune serum intraspinally in 2 meningitis cases; the dose of 16 cc. was repeated three times on alternate, once on successive days. The serum was obtained from an individual who had been immunized eight years previously to several strains of brucella with no subsequent injections of vaccine. In 1938, Poston and Menefee gave 250 cc. of citrated blood intravenously from this same donor and thought the patient's rapid improvement was initiated by this treatment. Of course ordinary convalescent serum has been tried numerous times according to methods similar to those employed in measles and other diseases.

Antiserum.—Goat antiserum, developed by Foshay and his associates, was reported upon by them (Wherry, O'Neil and Foshay, 1935), as employed in 26 cases by widely scattered physicians. More recently, Flippin has used a bovine serum in 5 cases. These serums were thought to have been useful.

Chemotherapy.—All the dyes have been employed intravenously, perhaps most frequently acriflavine (trypaflavine); Debono (1939), in Malta, thought this drug was effective in about 25 per cent of early cases, in doses of 10 to 15 cc. of 2 per cent solution every two or three days for 3 or 4 doses. Neoarsphenamine has been employed as in syphilis, and fuadin as in bilharziasis, but the record of these agents is not brilliant. Abbott *et al.* (1937) used 10 cc. of the 1:1000 solution of metaphen intravenously in 10 cases, giving injections daily for a week and then biweekly when indicated; they thought the treatment worthwhile.

Latterly the sulfonamides have been on trial but their record is not as brilliant here as in some other diseases. To be sure, the early reports, usually of the result in only a single case, were all favorable, but more recently failures have begun to be reported, especially by those familiar with the fluctuating course of this disease. Bynum (1939) failed in 6 cases, Debono (1939) in 25 cases, Huddleson (1939) in 15 cases. I do not mean to imply that the record of the sulfonamides is upon the whole bad in brucellosis (indeed, Horn, 1940, reviewing 83 cases in the literature and adding 54 of his own, concluded that the chances of sulfanilamide favorably influencing the disease are two to one), but there is no begging the question that they have not been brilliantly successful. Surely the following statement of Harris (1943) is one of the most equivocal in all of medical literature: "The sulfonamides are of value in terminating the acute illness but not uniformly so, nor are the patients necessarily cured."

I have not seen any report in which penicillin was shown to have an effect on the course of brucellosis.

CHICKENPOX

(*Varicella*)

Chickenpox is an acute infectious and highly contagious disease of unknown etiology, which attacks nearly all children at some time during their early years. Several serious students are at present attempting to show a causal relationship between it and herpes zoster, but they have not yet succeeded. The malady is characterized by the sudden appearance of a vesicular rash usually without any prodromal or accompanying constitutional symptoms; when the latter do appear they are extremely mild. The rash may be differentiated from that of smallpox (a feat not always so easy of accomplishment as this glib statement would indicate!) by the fact that it begins on the back, or some part of the trunk whence it spreads to the whole of the body, including the scalp, but is seen on the face and palms and soles only occasionally, and then to the extent of only a few lesions; that several stages of the eruption may be seen at one time, to wit, erythematous maculopapules, clear vesicles, clear vesicles surrounded by an erythematous corona ("a dewdrop on a rose petal"), turbulent vesicles, somewhat pustular vesicles, and crusted vesicles; by the fact that these vesicles are more nearly unilocular than in smallpox (collapsing more completely after a single needle puncture) and that they are more irregular in outline than the smallpox vesicle and are not umbilicated. Anomalous forms of the rash are occasionally seen. Johnson (1940) reported a complete postmortem examination on an infant in which areas of focal degeneration showing similar pathologic changes to those demonstrable in the skin were found in the esophagus, pancreas, liver, renal pelves, ureters, bladder and adrenal glands; Oppenheimer (1944) reported the finding of similar disseminated lesions in one of the rare cases of congenital chickenpox, of which less than a dozen have been recorded. In chickenpox there seems to be a strong stimulus to lymphocytic activity but, according to Holbrook (1941), a typical blood formula for the disease has not yet been described.

The incubation period varies from four to more than twenty days but most cases develop twelve to fourteen days after exposure. One attack practically always protects for life; therefore, since most mothers are immune and transfer the immunity placentally, chickenpox in the newborn is rarely seen. So far as is known to me there is no racial immunity to chickenpox. In 1936 the disease was severely and fatally epidemic among the natives in French Cameroun, and Mumford and Mohr (1944) stated that it had appeared as a highly fatal epidemic disease in the Marshall Islands in 1887.

The disease was first described by Ingrassias (1553), but the most famous of the early treatises is that of Heberden (1767), which contains his original illustrations. Attention was first attracted to the possible relationship of chickenpox to herpes by Bokay in 1892.

THERAPY

Chickenpox is constitutionally a mild affair and usually requires no treatment. The eruption occurs during two to five days and usually most of the scabs are off in a week but sometimes a few cling to a tough central root for several weeks. After-scarring is very infrequent. For control of the itching recourse may be had to the measures employed in smallpox. Bullowa and Wishik (1935) tabulated complications in about 5 per cent of 2534 cases in hospital but the incidence is certainly lower in home-treated cases. The most

serious though very rare occurrences are doubtless massive skin gangrene and the form known as varicella pustulosa in which most of the pocks become furuncles or solitary abscesses. In these cases, of course, sepsis or bronchopneumonia is much to be feared. The lesions should be frequently cleansed with boric acid solution, or perhaps it is preferable to immerse the patient for fifteen to thirty minutes several times daily in a warm bath containing a level teaspoonful of potassium permanganate to 4 gallons of water. The easiest way to prepare such a bath for the first time is to fill the tub to the desired point from a pail of known capacity. It is well to have the tub washed out afterward, to prevent permanent staining, with a solution of ½ ounce of oxalic acid (poisonous!) to the quart of water, rinsing well afterward. I have seen no record of the employment of the sulfonamides in such cases. Complications of the nervous system, such as encephalitis and encephalomyelitis, have been reported but are extremely rare and usually of good prognosis, though Waring *et al.* (1942) reported the case of a forty-year-old male who died with complicating pneumonia, encephalitis and nephrosis. Gangrene and extensive necrosis around the site of the pocks is a very serious but fortunately extremely rare complication.

PROPHYLAXIS

Vaccination.—The vaccination of exposed individuals with the contents of chickenpox vesicles was introduced in Germany by Kling in 1913, but it has not been the consensus that it has much protective value; however, a favorable report (von Gulácsy, 1933) still appears now and then. The contents of a fresh vesicle, drawn up into a capillary tube, are introduced by the puncture or intracutaneous injection methods in all details precisely as in smallpox vaccination. The "take" occurs between the eighth and thirteenth days—papule, vesicle, crust and possibly scar.

Convalescent Serum.—The studies of Gordon and Meader (1929) indicated that pooled whole convalescent serum is highly protective if obtained within one month of the appearance of the donor's eruption and stored not longer than four months, the dose being 4 to 10 cc. intramuscularly and severe reactions apparently not occurring. However, Lewis *et al.* (1937) failed to find such convalescent serum of the least value in protecting against the disease, and the several studies of McGuinness (1943) and his group indicated no higher value for reconstituted pooled lyophile serum.

COMMON COLD

(*Catarrhal Fever, Acute Catarrhal Nasopharyngitis*)

The symptoms of this virus infection, of which most of us experience two or three attacks each year, are very simply listed: typical "cold in the head," headache, sore throat, chilliness, impairment of taste and smell, a nonproductive cough with considerable soreness behind the sternum, fever, malaise, and so on. Colds are highly contagious and have an incubation period of between twenty-four and thirty-six hours. The infected individual seems able to infect others four to six hours before he himself develops symptoms but thereafter he remains infectious for only the first day or two of his own attack. The resistance to reinfection which develops as the result of a cold is well known

to be of short duration; Paul and Freese (1933), studying the matter in an isolated Arctic community, estimated the duration of this immunity to be not less than twenty-three days with an average of about seven weeks. It was demonstrated a number of years ago that the virus of the common cold promotes and furthers infection of the respiratory organs by pathogenic organisms such as pneumococcus, hemolytic streptococcus, staphylococcus, and the like, and it is now recognized that it facilitates the distribution of these bacteria in the community and establishes a background for the occurrence of severe outbreaks of respiratory diseases. We are almost completely ignorant of the factors responsible for the sudden massive outbreaks of colds; in the United States the three main peaks of incidence each year are in January and February, April and May, and September and October. According to Keefer (1943), the epidemic occurring in the spring tends to be the mildest and that occurring in January and February the most serious as measured by absence from work and severe complications.

THERAPY

Relief of Discomfort.—In the beginning some such capsule as the following, to be repeated every three hours with the patient kept in bed, will greatly relieve discomfort:

℞	Acetylsalicylic acid	gr. v	0.3
	Phenacetin	gr. iiss	0.15
	Caffeine citrate	gr. ss	0.03

In a large-scale comparative study of therapeutic measures in the Navy during War II, Short *et al.* (1944) found the use of this combination of drugs very effective but sometimes objectionable since it tended to produce drenching sweat, necessitating frequent change of garments, and the danger of chilling; Short's dosage, however, was somewhat greater than that in the capsule formula above.

A "hot toddy" of whiskey, sugar and hot water is of value to many patients in the beginning, causing a mild diaphoresis, a considerable amelioration of the general bodily weariness and a grateful lessening of apprehension. The old-fashioned Dover's powder (powder of ipecac and opium, N.F. VII) used very much to be employed for this purpose; the ordinary single dose (in capsule) of 5 grains (0.3 Gm.) Diehl (1933) found may be safely and well increased to as much as 15 grains (1 Gm.), but since he observed that powdered opium alone in equivalent dosage was equally valuable he concluded that the diaphoretic action of the ipecac was unimportant. Furthermore, out of his apparently well controlled study of the effects of opiates on the common cold emerged the fact that a combination of ¼ grain (0.015Gm.) of codeine sulfate and ¼ grain of papaverine hydrochloride was more valuable than any other preparation in inducing prompt decrease or complete disappearance of the nasal discharge and congestion, and this without the unpleasant dryness that usually occurs when atropine is used for this purpose. Accompanying laryngitis, pharyngitis and tracheitis were not materially relieved. The following is his dosage scheme in terms of single capsules each containing the two drugs as above stated:

75 to 99 pounds:	1 after breakfast; 2 at bedtime
100 to 129 pounds:	1 after breakfast; 3 at bedtime
130 to 169 pounds:	1 after breakfast; 1 after lunch; 3 at bedtime
170 pounds and over:	1 after each meal and, depending on weight, 3 or 4 at bedtime.

Unpleasant symptoms such as nausea, dizziness, headache and fainting were infrequent accompaniments of this medication; addiction to either of the drugs is not to be feared. This codeine-papaverine combination is commercially available in tablet, capsule and elixir form as "copavin" and is very much employed.

Another method of relieving the feeling of fulness in the head is to cause the patient to breathe an atmosphere that is saturated with moisture. A teaspoonful of the following inhalant may be vaporized by pouring scalding water upon it in a previously heated cup; with his head low over the cup, and a large towel enclosing both, the patient breathes with mouth open. Sometimes the feeling of stuffiness is only increased by such a steamy inhalant; exposure should be avoided for an hour after its use. The housewife will be grateful if forewarned that both the cup and spoon are very difficult to clean after their employment for this purpose.

℞	Oil of pine needles	ʒiv	15.0
	Tincture of benzoin to make	℥iv	120.0

If desired, creosote (½ drachm, 2 Gm.) may be added to the above, but as it is a mixture of phenols there is some reason to believe that if used too freely it may cause some damage to the kidneys. For bedridden patients, Means and Lerman found it convenient to place the above ingredients in an ordinary teakettleful of boiling water on a chair beside the bed; a length of large rubber tubing is stuck onto the spout and the patient takes the free end into his mouth, thus getting the full effect of the medicated steam without having to put his neck into an uncomfortable position.

Nowadays the benzedrine (amphetamine) inhaler is much employed for the relief of nasal congestion, but some patients react unfavorably with restlessness and secondary reactions of the mucosa. Kully (1945) referred to the "suggestive coincidence" that in a series of 640 of his patients with acute sinusitis 85 per cent had used nasal vasoconstrictors for several days prior to the onset of the sinusitis (see *Acute Paranasal Sinus Involvement* for further discussion).

For the relief of the substernal tightness and pain, a mustard poultice is frequently employed. This is conveniently made by spreading between two layers of thin muslin a paste made by mixing equal parts of ordinary household mustard and wheat flour stirred together with warm water. Prepared plasters which are very convenient to use may be purchased at drug stores, but these too should be dipped in warm and never in hot water, for the irritant property in mustard is developed through enzyme action and the enzyme is killed by heat. Whether the prepared or home-made article is used, it should be left in place over the upper part of the sternum until the skin becomes quite red, which usually requires from fifteen to thirty minutes.

Combating Cough.—Among the expectorants ammonium chloride is probably the most certain in its action (but *not* if used as enteric-coated tablets). Some such preparation as the following, which contains approximately 8 grains of the drug to each teaspoonful, is usually effective if given every *two* hours:

℞	Ammonium chloride	ʒiv	15.0
	Syrup of citric acid	℥j	30.0
	Water to make	℥iv	120.0

Frequently the drug is used as in the following prescription, in which the "brown mixture"—containing too little of its active ingredients (paregoric,

tartar emetic and spirit of ethyl nitrite) to be usually effective alone—very satisfactorily supplements the action when used as a vehicle:

℞ Ammonium chloride..... ʒiv 15.0
Compound mixture of opium and glycyrrhiza (N.F. VII).... ℥iv 120.0
Label: 1 teaspoonful every two to three hours.

A sip of pineapple juice after ammonium chloride very nicely overcomes th taste. If the drug nauseates, sodium citrate may be substituted in 10- to 15-grain (0.6–1.0 Gm.) doses; it has the added advantages that it is a diuretic and indirectly an alkali. Or 2 or 3 drops of a saturated solution of sodium or potassium iodide may be given in water every two hours, but bearing in mind the frequent occurrence of iodism, the interval between doses should be lengthened as soon as possible. The syrup of hydriodic acid is well taken by children in doses scaled down from 1 drachm (4.0 Gm.) according to size and age. However, bronchial irritation may be aggravated by the iodides. Syrup of ipecac is frequently used also. The best dosage with which to achieve expectorant action without causing nausea is 5 to 8 minims (0.3–0.5 Gm.) every two hours.

℞ Syrup of ipecac..... ʒiv 15.0
Aqueous elixir of glycyrrhiza to make..... ℥iv 120.0
Label: 1 teaspoonful every two hours.

For a child, with its preference for sweets, the syrup of glycyrrhiza had best be substituted, or any of the other vehicles liked by children may be used: syrup of raspberry, syrup of tolu balsam (vanilla-like flavor), syrup of cacao (chocolate flavor), syrup of cinnamon. Evidently the profession, at least in England, is very fond of the use of iodides and ipecac in cough, for when Alstead (1939) questioned their value he was very tartly reprimanded in a letter "to the editor" of the Lancet.

When it is felt that a full effective amount of an opiate should be incorporated in the cough mixture, some such prescription as the following may be written:

℞ Pantopon..... gr. iss 0.10
Syrup of cacao to make..... ℥iv 120.00
Label: 1 teaspoonful every three hours (for adults).

The pantopon is present here in 1/20-grain (3 mg.) doses. Dilaudid in the amount of ½ grain (30 mg.) could be substituted for pantopon; the teaspoonful dose would contain about 1/64 grain (1 mg.).

The following are satisfactory codeine prescriptions:

℞ Codeine phosphate..... gr. viiss 0.45
Ammonium chloride..... ʒiv 15.00
Syrup of citric acid..... ℥j 30.00
Water to make..... ℥iv 120.00
Label: 1 teaspoonful every three to four hours.

℞ Codeine phosphate..... gr. iv 0.24
Elixir of terpin hydrate to make..... ℥iv 120.00
Label: 1 teaspoonful every three to four hours.

The first of these prescriptions contains approximately ¼ grain (15 mg.) of codeine phosphate, the other ⅙ grain (10 mg.) per dose; it is well to bear in mind that elixir of terpin hydrate contains about as much alcohol as does whiskey. A larger amount of codeine may be needed, though Davenport (1938)

found that in most instances in tuberculosis sanatorium practice the smaller doses suffice.

Cathartics.—And now the question of the initial cathartic. I well remember my late professor of medicine as, with serious mien, he said to us many a time in class, "Gentlemen, I *always* prescribe calomel on the first visit," and then, with a sly twinkle in his eyes, "or on the second." And doubtless he did just that. But why? Certainly if a cathartic is to be used at all it had best be calomel, or at least not a saline, for Macht and Finesilver conclusively showed in both laboratory and clinic that the taking of a saline cathartic prevents the absorption, and therefore the effect, of other drugs taken simultaneously or quite some time later. But why give a cathartic at all when we know the debilitating effect of a purge even in a well individual? Some time ago the following facetious letter, which has caused me much amusement, appeared in the Journal of the American Medical Association; I quote almost *in toto*:

"*To the Editor:*—I appeal to the fountainhead of medical knowledge for information on a subject of greatest personal and community importance. Shall I take a physic? And shall I give a physic to practically all my patients? I have not taken a physic for nearly fifteen years and am in perfect health. My intestinal exit operates as faithfully as the inlet, with an almost unvarying ratio of three to one. Traffic occasionally slows up a bit and as a consequence terminal unloading facilities may be put to some test, but this is never extreme and there have been no failures nor needed repairs. Once in a long time I have a cold but in no instance has a cold ever slowed up deliveries. Years ago I always took a physic for my colds, which always did two ugly things to me: They always gave me a bellyache and disturbed my regular evacuating habits. My colds without physics are just as brief as those subjected to the foregoing complications.

"Now as to my patients. They all want a 'thorough cleaning out' and 'a change in diet.' Regarding diet, I am frequently distressed with my inability to supply new formulas and combinations; but I am not now asking for any relief in this particular. However, I do want enlightenment on the contention that if the patient suddenly shows a little fever or a subnormal temperature or restlessness, or tympanites, or a collapsed abdomen, or frequency of bowel movements or a total stoppage, or numbness of the first three fingers on the right side, or anorexia, or a gluttonous appetite, or nausea, with or without vomiting, or a sudden dislike for the male parent, that such a patient should at once have a physic And if so, what? and when? and how long?

"A new treatise on skin disease just came to my notice, and in going through it in a quick review, my memory may not serve me perfectly but I can now recall just one condition that did not require a 'purge,' 'a physic' or a complete overhauling of the eliminating machinery, and that was freckles. I was pleased, as I have freckles and it may be safe to go right on neglecting my bowels as heretofore with safety. I have no more trouble keeping my bowels regular than my nose Roman, and I have about come to the conclusion that, colds or no colds, I need plastics for my nose just as frequently as physics for my bowels, and that's that.

"Such limited reading of last editions as I do gives me scant support for my aversion to purges and 'thorough cleaning out of the intestinal tract.' My frequent contact with physicians convinces me that I do far less cleaning out than they do, and when it comes to toning up a liver with laxatives I am almost a total failure. I try. In this community one simply must be able to do considerable in the way of toning up livers. It seems that we live in the toneless liver belt; and since Marshall Field established that the customer is always right, we must tone 'em up as per general request, or they will get another toner. I do not know whether the people or the physicians established this belt, but it's here all right and we live in the center of it. . . . At a recent meeting of our society I informed my confrères . . . that I was making no effort to transform my 'cold' cases into dysentery cases, and now I wish I had not for I fear I lost caste or something.

E. O. Harrold, M. D."

Well, well! Smith and Baier (1939) put the matter to the test in a study at an Army post early in War II, employing castor oil and magnesium sulfate in 520 cases with 493 untreated controls (all patients having temperatures rang-

ing between 100° and 102° F.); they felt that the use of the cathartics actually prolonged the attack.

Fluid Allowance.—As in all other fevers, water should be liberally given. The patient should take at least ½ tumblerful every hour while awake. It is often easier to induce the taking of this much fluid if it is given in the form of lemon- or orangeade. This fruit juice, since it is potentially alkaline, also helps to meet what is generally looked upon as a definite indication, namely, the necessity to overcome acidosis. Whether this acidosis actually exists, or whether the effectiveness of "alkalinizing the patient" is only an unfounded clinical tradition, is not definitely answered so far as I am aware. A quarter-teaspoonful of sodium bicarbonate added to the glass of lemonade will help in accomplishing this desired result.

In leaving this subject of fluid allowance, perhaps it should be pointed out that there is a rather large group of physicians, apparently quite orthodox fellows in all other respects, who doubt the advisability of making the patient fairly swim in water unless he has shown some previous evidence of being in a state of dehydration; however, since Harrold (1936) has pointed out that no one ever heard a fish sneeze, the practice of "pushing fluids" probably has a rational basis.

Diet.—In the beginning, when the patient is feverish and feeling quite ill, he will likely be uninterested in taking more than the fruit juice referred to above; if this is fairly well sweetened he is of course getting a bit of nourishment. Ideally, if the siege threatens to last a number of days, it would be well to have him drink a quart of milk (reinforced by about a half pint of cream if he will accept so much "richness") during the twenty-four hours and offer him a couple of soft-cooked eggs and a small portion of cooked cereal at one or other of the usual mealtimes. See Index for an eggnog recipe. Later, in leading back to full diet, reduce the milk and add small amounts of bread and butter, lean cooked meat, and a bit of green vegetables or buttered baked potato if the aroma of that will tempt him. Occasionally a patient with grippe will develop a quite voracious appetite after a few days, a circumstance which we often meet by denying him all he wants because he is "lying inactively in bed," but Davis' (1934) studies indicated that perhaps in infants and young children at least our counsel of abstemiousness may not be so wise. In her work in a nursery in which, regardless of the height of fever, the youngsters were allowed to continue the choice of their foods during the course of colds and tonsillitis, she not only confirmed the well-known fact that appetite decreases twenty-four hours before there are any other signs of illness, but also observed that twelve to twenty-four hours before the fall in temperature or improvement in signs there was a sharp increase in desire for food. A child with high fever and several days' lack of interest in his food would suddenly sit up when his tray came in and eat heartily, with second and third helpings, of meat, potatoes and vegetables; no digestive disturbances resulted and convalescence followed predictably on the next day. It is interesting also that regardless of their predilections when well, these children turned with enjoyment to raw beef, beets and usually carrots when recovering from acute upper respiratory infections.

Sulfonamides.—The ordinary uncomplicated cold runs a mild afebrile course and clears up in four to seven days. Though having no mortality associated with it and oftentimes not even greatly incapacitating the patient, it may nevertheless cause some measure of debility for a considerable period of

time and therefore is of great economic importance. The more severe cold which is complicated by secondary bacterial infection involving the sinuses, the middle ear, the mastoid, and so on, is a serious matter indeed and therefore any agent which could be shown capable of preventing with fair regularity the bacterial complications of ordinary colds would be a welcome addition to our armamentarium. Sulfadiazine has had the most extensive trial in this connection, with results which will be discussed below.

Effect upon the Uncomplicated Course of the Disease.—The findings in three principal studies require to be recorded. Rusk and van Ravenswaay (1943), in an Army camp during War II, gave to 317 patients an initial dose of 3 Gm. and subsequent doses of 1 Gm. every four hours until convalescence was established or nonimprovement in protracted cases indicated that dosage should be stopped; acetylsalicylic acid, acetophenetidin and caffeine citrate were given to the 314 patients in the control group. No significant differences appeared, either in the length of the febrile period or in the period of hospitalization, in the two groups; and, very properly, the authors pointed out that the cost of the sulfadiazine treatment was approximately twenty times as great as treatment with simple analgesic capsules, a cost differential which would probably be much greater in civilian life. Cecil *et al.* (1944) followed 72 colds in 66 persons; 48 of the colds were treated with sulfadiazine 1 Gm. three times daily by mouth for four days, while 24 of the colds were untreated as controls. They found that the clinical course of the treated colds showed no striking difference from that of the controls and therefore expressed themselves as opposed to the routine use of the sulfonamides in the treatment of the common cold. Siegel (1944), after a carefully controlled study extending over several years among highly susceptible institutionalized feeble-minded children, was able to say only "the illnesses were milder, on the whole, in the drug-treated groups than in the untreated groups, with the exceptions noted in outbreaks of uncomplicated infections presumably of viral origin and in sporadic infections during the period studied. The beneficial effects were attributed to the bacteriostatic action of sulfadiazine on the susceptible bacteria primarily or secondarily involved"—or, when the colds were of the ordinary uncomplicated sort, no advantage accrued from the use of sulfadiazine.

Effect on Incidence of Complications.—The principal study to be considered in this connection is that of Dolowitz *et al.* (1943), of the Johns Hopkins Hospital, who treated 59 members of the nursing staff with sulfadiazine and left 44 as untreated controls. They administered sulfadiazine by spraying the nose and throat eight to twelve times daily for three days and five to eight times daily for two or three additional days with a 2.5 per cent solution of sulfadiazine in 8 per cent triethanolamine solution. Some patients objected to the taste of this spray, others complained of the irritation it caused around the external nares (the latter said to be prevented by frequent application of cold cream and petrolatum), and about 3 per cent of the patients developed sneezing and increased rhinitis as a result of the use of the spray; however, Dolowitz *et al.* seemed firmly convinced that by using the drug in a spray rather than in the form of tablets to be swallowed they obtained a much better inhibition of the growth of organisms in the sprayed area. The results recorded in this study were the following: sinusitis in treated group 9.7 per cent, in control group 30 per cent; otitis media in treated group 1.8 per cent, in untreated group 4.5 per cent; laryngitis in treated group none, in untreated group 2.3 per cent; sore throat in treated group none that developed during

treatment, in untreated group 10 per cent; cough developing during treatment in treated group 8 per cent, in untreated group 44 per cent. A more recent but much less detailed study was that of Faust and Simmons (1944) in one of the Army camps. In this study 4 Gm. of the drug were given initially by mouth and 1 Gm. every four hours thereafter as long as seemed indicated. One hundred and thirteen patients were so treated and 87 were given analgesic capsules and used as controls. The complications which developed in these two groups were bronchitis, tonsillitis, laryngitis, inflammation of the ear drum and sacro-iliac pain, and the average hospital stay of sulfadiazine-treated cases with such complications was said to have been 6.2 days while that of the untreated controls was 9.9 days.

Summary.—I do not know what to make of the above evidence except the following: (*a*) that the routine employment of sulfadiazine will not affect the course or duration of an ordinary mild common cold; (*b*) that it will, however, to a considerable extent reduce the incidence of bacterial complications; and (*c*) that the cost of this therapy is an item of some importance. Cecil *et al.* stated that on the basis of their experience they would restrict the use of the sulfonamides to very few selected cases, such as those in which the history reveals an almost invariable and severe secondary infection following the cold, and that would seem very good advice to follow under ordinary circumstances in peace-time civilian practice.

Patulin.—This is the name given to a substance obtained as a metabolic product from the filtrate of cultures of *Penicillium patulum*; the active principal of this substance has been isolated and crystallized and its chemical structure has been defined. It seems to be less effective *in vitro* against gram-positive organisms than penicillin but more effective against gram-negative ones. Raistrick *et al.* (1943) reported clinical trials of patulin in the treatment of common colds in which the agent was used in buffered aqueous solution and administered every four hours in dilutions of 1:5000 to 1:20,000, either spraying it on the nose and throat or douching the nose or sniffing it. It was said that 58 per cent of 95 patients receiving patulin during the first few days of an uncomplicated cold were "cured" within forty-eight hours; 9.4 per cent of 85 control patients in whom only a buffer solution without patulin was employed were benefited within the same period. These data were reviewed by Greenwood, the well-known statistician, and were found to be statistically significant. However, just one week after the publication of the paper by Raistrick and his associates, which caused quite a stir in the public press in England, Stuart-Harris *et al.* (1943) stated that in their hands patulin had been without any effect, since in 100 cases of ordinary afebrile common cold in which alternate cases were treated and not treated the proportion of those showing clinical improvement was substantially the same in both groups. The subsequent studies of Stansfeld *et al.* (1944) and of the Patulin Clinical Trials Committee, reporting in England in 1944, both failed to yield any evidence of the effectiveness of patulin in the treatment of the common cold. So the hopes raised by the early reports with this agent seem to have been completely dashed.

ACUTE PARANASAL SINUS INVOLVEMENT

The anterior group of sinuses—the frontal, the anterior ethmoidal and the maxillary antrum—open into the middle meatus beneath the middle turbinate; the posterior group—posterior ethmoidal and sphenoidal—open far

back and high up above the middle turbinate. While the former are more often involved than the latter, it would seem advisable for the general practitioner to consider all the sinuses equally affected in any given case, for he can hardly show preference to one or the other in the application of his nonspecialized therapy, and he will nearly always be actually justified in his assumption, since infection in cavities above or below the ones suspected of being principally involved is doubtless an important factor in preventing quick recovery in the majority of instances. Bearing in mind that most patients recover spontaneously in one to three weeks except when the attack occurs during an influenza epidemic of some virulence, treatment should simply have the following objectives: to clear the passages, reduce congestion, attack the causative organisms if this is feasible, with resort to surgery only when imperatively necessary.

Clearing the Nasal Passages.—Hawking back into the nasopharynx and then expectorating the accumulations is less dangerous than nose-blowing but of course young children cannot perform this act. Some of the exudate can be got out through the nostrils by medicine dropper suction; one should proceed very cautiously and gently in the application of more forceful mechanical methods than this if secondary engorgement is to be avoided. If the nose must be blown it should be done with both nostrils wide open; Parkinson (1935) well emphasized the fact that the familiar method of blowing while the nostrils are partially closed with the fingers, or while one is completely occluded with the other wide open, can force secretions back into the sinuses or out into the eustachian tubes. In any case, blow gently!

For best drainage it is probably advisable to have the patient at least partially upright with the head comfortably supported in a position of slightly forward flexion. Layton (1935) made the point that too great flexion, however, is likely to increase the headache; he felt that unless otherwise too ill the patient does better in an armchair than in bed. Keeping the room warm and the moisture as high as possible are helpful measures. The use of a steamy inhalant (see "Relief of Discomfort" in this present article) is also indicated, but in view of the findings discussed below (under "Sprays and Drops") it may be advisable to employ merely steam alone without the addition of any medicinal ingredients.

Among conditions favoring obstruction to drainage and thus potential prolongation of the siege are deflected septum, hypertrophied turbinates and nasal polypi. Howarth (1935) felt that a careful rhinological examination—presumably by a specialist—is a necessary preliminary to any forecast of the duration of the condition, but unfortunately removal of these obstructions does not by any means always effect amelioration. Similarly there is disagreement among rhinologists regarding the advisability of routinely removing simply hypertrophied tonsils and adenoids in these cases, though the consensus seems to be that if "septic" they should come out.

Reducing Congestion.—It is probable that the most important aim of treatment is to facilitate drainage from the sinuses by reducing congestion of the mucous membranes about the openings into the meatus and it is just this thing which we are not often able to accomplish satisfactorily. Not that the mucosa cannot be shrunk—nothing is easier really—but to do it without causing a reaction of turgescence or greatly slowing or stopping entirely the movement of the cilia of these membranes, there lies the difficulty. Investigation of the cilia which sweep all secretions back toward the esophagus has disclosed that any measures which retard their movement are apt to postpone

the patient's recovery from an acute attack or convert the condition into a case of chronic sinusitis. The following measures are discussed with this in mind.

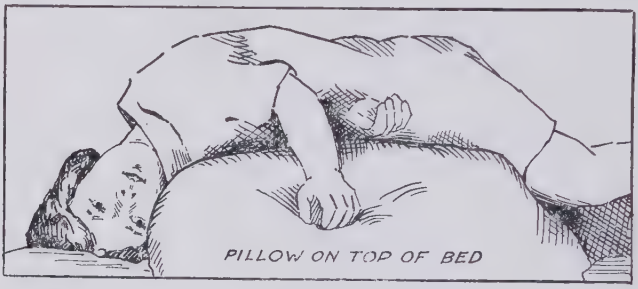
Sprays and Drops.—The investigations of a number of workers since 1933 (see Lierle and Moore, Proetz, McMahon, Fenton and Larsell, Walsh and Cannon, and Cannon, in Bibliography) have indicated a number of surprising things with regard to heretofore commonly employed drugs. In brief the observations are as follows: (*a*) Physiologic solution of sodium chloride has no effect on either cilia or epithelium. (*b*) Both tap and distilled water promptly stop ciliary activity and liquid petrolatum (albolene) markedly slows it. (*c*) From 0.5 to 3 per cent of ephedrine in physiologic solution of sodium chloride does not affect the cilia. (*d*) Epinephrine (adrenalin) 1:5000 to 1:1000 in normal saline slows or paralyzes and so does cocaine in more than 2.5 per cent strength. (*e*) Mild silver proteins of the type of argyrol and neosilvol are incompatible with the salt solution and when used in water definitely slow the ciliary activity. Ten per cent concentration of these drugs in contact for twenty minutes with the mucosa of the frontal sinuses of the dog caused edema and intense cellular concentration throughout the mucosa and actual fragmentation of the columnar epithelium. (*f*) Eucalyptol, menthol, thymol, zinc sulfate, mercurochrome and merthiolate all cause slowing or paralysis of ciliary activity depending upon their concentration. (*g*) Oily vehicles are dangerous from the standpoint of liability to induce lipoid pneumonia, and some much used agents, such for example as the mild silver proteins, are also prone to cause comparable pulmonary tissue reactions.

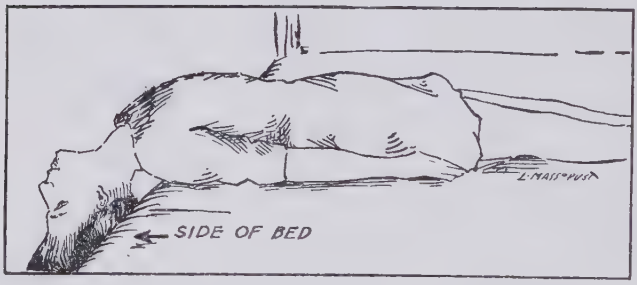
Therefore, of the astringents principally used—cocaine, epinephrine (adrenalin), zinc sulfate and ephedrine—only the latter would seem to be advisable from the standpoint of effective shrinking of the membrane without harmful action. The following prescription, useful as either spray or drops, contains 1 per cent of the active drug in 0.9 per cent saline; it may be sterilized by boiling and will then keep for many months without the addition of a preservative:

℞	Ephedrine sulfate	gr. xx	1.2
	Sodium chloride	gr. xvij	1.0
	Water to make	℥iv	120.0
	Label: Use as nose spray or drops as directed.		

Parkinson (1936, 1939) strongly advocated the "lateral head-low posture" in introducing drops into the nose. Reference to the diagrammatic sketch will show how this position differs from the common one in which the patient lying across the bed drops the head back against the bed's side in order to approximate the upside down position; a young child must be forcibly held thus and to propose putting him into the position a second time "is notice to start a riot," as Reese (1934) well said. The lateral head-low posture is less formidable and more nearly comfortable. Parkinson sprays the nose at intervals of several minutes with the ephedrine solution in order to accomplish as thorough ventilation as possible; then, the patient placed in the lateral posture, at least one dropperful of the solution is instilled into each nostril, the position being held for three to five minutes during which time mouth breathing prevents the fluid from being drawn into the pharynx. Finally the head is rotated to face downward and the patient remains thus for a few more minutes to allow the fluid contents to be expelled from the nose. These treatments can be repeated several times daily with spraying in the interim.

Everyone admits, I think, that ephedrine will vigorously contract the arterioles and produce a period of ischemia and shrinkage of the membrane which is ideal for drainage, but many men have given up the use of the drug because of the stinging sensation in the beginning and the subsequent reaction of engorgement; these effects, however, are said not to occur if the drug is applied in physiologic saline solution as in the prescription above. Benzedrine (amphetamine), in the well-known inhaler, may be used satisfactorily by some patients but others are made very restless by the drug and suffer from sleeplessness throughout the night if they have sniffed at any time during the evening. Peters and Faulkner (1939) studied the effects upon the pulse, blood pressure and electrocardiogram, as well as the subjective symptoms, of 57 patients with various types of cardiovascular disease; each patient took five deep inhalations into each nostril in the course of two minutes. Their conclusion was that neither heart disease nor hypertension *per se* contraindicates the





use of the benzedrine inhaler but that it should be used cautiously if at all in patients with angina pectoris since in occasional cases it may precipitate an attack. I would point out that their findings indicate nothing with regard to frequent inhalation over a long period.

A prescription for drops, much used by rhinologists (Reese), is the following:

℞	Cocaine (alkaloid)	gr. j	0.06
	Camphor	gr. j	0.06
	Oil of cinnamon	♏j	0.06
	Liquid petrolatum to make	℥j	30.00
	Label: Drop into nose as directed.		

The amount of cocaine here (less than 0.25 per cent) is not sufficient to check ciliary action but enough to cause some slight shrinking, and its presence prevents refilling of the prescription without permission. But the oils have adverse action on the cilia (see above), and Walsh and Cannon (1938) pointed out

that they may quickly make their way into the lungs and there set up a lipoid pneumonia; one wonders if merely the cocaine in normal saline might not be just as effective without having any deterrent action—a prescription such as the following:

℞	Cocaine (alkaloid)	gr. j	0.06
	Sodium chloride	gr. ivss	0.27
	Water to make	℥j	30.00
	Label: Drop into nose as directed.		

The introduction of cotton-tipped applicators or tampons soaked in stronger cocaine solutions seems inadvisable in the present state of our knowledge; at least the general practitioner may well talk himself past this point for if the patient gets on nicely without these ministrations he is likely to overlook the omission, while if he must ultimately be referred to one of the gentlemen who specialize in the treatment of these cases in the chronic stages one may be sure that he will thenceforward be probed to repletion.

Attacking the Causative Organisms.—Even though the older antiseptics had not been shown to be detrimental to ciliary action there would be no true rationale in their use here for the reason that sterilization of no mucous membrane can be accomplished by such local applications. They give rise to an undesirable secondary reaction also, which Reese has well dubbed "mucosal diarrhea." And furthermore, argyrol dropping has long been traditional in most families; when the doctor is finally called he is expected to know several tricks far superior to that. The newest fad is of course to use a spray of 5 per cent sodium sulfathiazole, but this spray sometimes causes irritation and even necrosis of tissues has been reported; furthermore, if it is employed only a two days' supply should be prescribed for the reason that decomposition occurs rapidly and the decomposed is even more irritant than the fresh solution. Turnbull *et al.* (1943) claimed that the addition of sodium sulfite to the solution made it stable to light, air and heat and that the further addition of *dl*-desoxyephedrine hydrochloride increased the activity of the sulfonamides; it was further claimed that the combined use of these three agents allowed ciliary action "to continue for a long period of time." This mixture is commercially available. Sulman (1943) reported the satisfactory employment of a commercially available preparation of 5 per cent of the microcrystals of sulfathiazole in a 1 per cent aqueous solution of paredrine hydrobromide.

I do not believe that the value of any vaccines, be they orthodox or the new undernatured bacterial antigens, has been shown as yet.

If the patient is suffering from any one of the vitamin deficiencies his resistance will be of course immensely improved if the missing factors are supplied, but we have no proof or even strongly suggestive evidence that the feeding of any of the vitamins in greater abundance than provided in the ordinary well-balanced diet is of the least value in promoting recovery. Likewise the malnourished individual requires building up but there are no magic essences whose administration will promote the equivalent of this slow process in shorter order.

The dry climate of inland mountainous regions is beneficial to some patients; others profit by a long ocean voyage or sojourning for a while on a warm seacoast.

The sulfonamides administered internally are of course being tried but the success attained so far has only been moderate. It is said that the occurrence

of a positive blood culture in acute sinusitis is extremely rare except as an indication of invasion of the stream from some other focus.

Surgery.—When, despite treatment such as outlined in the preceding pages, the pain and headache increase, temperature rises, and the surrounding tissues begin to swell, it is felt by many that resort to surgery should be had; at least otorhinologic consultation at this time may be to the advantage of the patient.

OTITIS MEDIA AND COMPLICATIONS

(Mastoiditis and Chronic Suppuration)

When infection spreads into the eustachian tube this passageway quickly becomes occluded by the swelling of its mucosa and products of inflammation accumulate thereafter in the infected atrium or lower cavity of the middle ear. In most instances it seems that the curtains of swollen mucous membrane which separate the attic with its contained ossicles from this lower space are not easily penetrated, so that rupture and escape through the less resistant ear drum take place if the inflammatory process continues for long or if pus accumulates quickly in large amount.

Early Treatment.—In the beginning relief of pain is indicated while waiting for the severity of the involvement to become manifest. Opiates seriously mask the symptoms and should not be used, but ear drops such as the following are much employed:

℞	Phenol	gr. xxv	1.5
	Glycerin	℥j	30.0

Label: Warm and introduce 3 to 5 drops in ear every 2 or 3 hours.

Hot applications, in the form of the electric pad, hot water bottle, or poultices will also bring much relief and aid in "pointing" the process. The linseed poultice (see Index) retains heat a long time but its weight on the ear is sometimes objectionable.

Incision (Paracentesis).—As pressure of the pus increases so does the pain and in young children fever often rises quite high; adults may remain afebrile but will complain of noises in the head and deafness on the affected side. The landmarks disappear from the ear drum, the light reflex is lost, and the drum becomes dark red and begins to bulge. Now arises the question, should incision be made at once? I know that the almost unanimous "yes" of the rhinologists seems to supply a very definite affirmative answer, but perhaps the point is a bit finer than this. Is it not true that the cases which rupture spontaneously usually do so before the practitioner has had much time to ponder the question to cut or not to cut, and that the frequent necessity to add an incision even after the rupture indicates a quite fulminant quality in these infections? Of course the query cannot be answered because "incise when it bulges" is so much the rule nowadays (even a normal infant's drum may bulge when it cries, you know) that opportunity is rarely given the slowly developing cases to subside as slowly again without benefit of surgery.

Local Anesthesia.—Curry (1936), of the Cook County Hospital, described the procedure as follows: "Equal parts of phenol, menthol, and cocaine hydrochloride are used. This thin paste is applied sparingly with a small cotton applicator to the bulging area of the ear drum. It is well to warn the patient that the first touch hurts. The swab is held in place as long as the patient can bear it, which is usually a few seconds. The same procedure is continued until

the applicator can contact the inflamed ear drum without much discomfort for a minute or two. The incision is then made through the bulging area of the ear drum, which should appear white if properly anesthetized, with a light paracentesis knife. If there is no bulging, the incision is made in the posterior quadrant of the ear drum. In certain types of influenza ears, the drum cannot be seen because of blebs. These can be opened only by guess. With gentleness and care, an experienced surgeon can insert the knife through the blebs and toward the ear drum until the point of the knife gently strikes the promontory without harm. I have found no need for extensive incision of the ear drum. If the tympanum continues to fill with pus, the small incision enlarges with the infection. If drainage is slight, the small or large incision closes quickly and another opening may be required."

General Anesthesia.—Ethyl chloride sprayed on an open mask over the nose and mouth is satisfactory for one experienced with this useful anesthetic; or vinyl ether (vinethene) may be used by the drop method. Of course nitrous oxide or ethylene is ideal but expensive and often unobtainable for a patient quarantined by the primary infection.

Treatment after Incision.—With the establishment of free drainage pain disappears and subsidence and resolution of the process occur fairly rapidly in most cases. The objects of treatment at this time are to facilitate evacuation of the seropurulent discharges from the middle ear, promote their removal from the external auditory canal and prevent irritation of the external ear. Rhinologists are divided in their allegiance to wet or dry methods of accomplishing these results, so I shall describe them both.

Wet Treatment.—Immediately after operation or rupture a gauze wick is carried in as far as the opening in the drum and replaced frequently during about forty-eight hours. Then irrigation is instituted with the following approximately saturated solution of boric acid as hot as can be borne (about 110° F.); the soda aids in dislodging a sticky discharge but may be omitted:

℞	Boric acid	ʒx	40.0
	Sodium bicarbonate	ʒx	40.0
	Water to make	Oij	1000.0
	Label: Use for irrigation of ear.		

The irrigations should be performed gently, with the ear held downward over a pan, and repeated three or four times daily. Between treatments a wick may be kept in the canal or the phenol-glycerin drops (see above) may be diluted with an equal quantity of boiled water and instilled. Some men prefer to swab the canal dry after the irrigation while others do nothing; a gauze pad may be applied over the external ear and conveniently held in place by a hair net tied under the chin.

If blockage takes place as indicated by return of the earache, a few drops of hydrogen peroxide are instilled to reestablish drainage.

Dry Treatment.—This consists in frequently wiping the discharges out of the canal with cotton-tipped applicators and the avoidance of irrigation, though in this method it is sometimes the practice to dip the swab in the following solution before introducing it into the ear:

℞	Boric acid	gr. xl	2.4
	Alcohol	ʒj	30.0
	Water to make	℥ij	60.0
	Label: Use in swabbing ear.		

Some men like to blow powder into the ear after the swabbing, believing that the dry powder lying against the drum attracts discharges through the opening; boric acid is used alone or combined with 1 per cent iodine, as follows:

℞ Iodine (Crystals) ..... gr. v 0.3
Boric acid ..... ℥j 30.0
Dissolve iodine in alcohol, make into paste with the boric acid and dry to a powder.
Label: To be used in ear as directed.

Protecting External Ear.—Dermatitis may arise as a result of the irritating effects of the discharges. Washing the ear once or twice daily with normal saline (in the home, a teaspoonful of salt to the pint of water) and keeping it covered with a layer of zinc oxide ointment U.S.P. will likely prevent this.

The Sulfonamides.—Bowers, in 1940, cited 231 cases of otitis media under daily observation at St. Luke's Hospital in New York. In the 113 cases in which chemotherapy was employed the average duration of the discharge was nine days; in the 118 untreated controls it was seventeen days—thus a reduction of approximately 50 per cent was accomplished. Again, in the matter of mastoidectomies, 387 cases were observed, in none of which the ear condition was of more than a few days' duration before admission; in 12 (5.7 per cent) of the 207 treated with chemotherapy mastoidectomy was necessary, whereas it had to be performed in 24 (11 per cent) of the 180 cases not so treated. Bowers said, therefore, that when the drug is given early, before mastoid softening occurs, the number of cases requiring operation is reduced one half. But that was in 1940, and since that time a considerable difference of opinion as to the advisability of using a sulfonamide in every case of acute otitis media has arisen. Woodward (1942) stated that the drop in the performance of simple mastoidectomies in the United States started before the advent of chemotherapy and could not be attributed solely to the use of the sulfonamides. Richardson (1942) reported in detail a series of 625 cases of acute otitis media followed from incision to healing and concluded that the decreased incidence of mastoiditis comes chiefly from the moral support to the surgeon that allows him to defer operation until nature heals the infection. Since the incidence of mastoidectomy in his series without sulfonamide compounds was only 5 per cent, he felt that this 5 per cent incidence must be materially reduced by chemotherapy in order to justify routine administration of a sulfonamide compound to every patient with acute otitis media. Upon the other hand, DeSanctis *et al.* (1942) concluded that the sulfonamides were of great value in their large series of cases, giving an incidence of 9 per cent of mastoiditis contrasted with 30 per cent in a group not receiving chemotherapy. Also in the series of Bilchick and O'Kane (1942), in which 40 patients were treated and 40 were left as untreated controls, the duration of discharge was reduced by one third in the treated group and the number who underwent mastoidectomy was reduced by over one half. Dysart (1944), in a review of the subject, stated that it is his own custom to give sulfadiazine early and in full doses to all patients with acute otitis media who show by temperature, pain, or other symptoms that their infection is more serious than the average.

So, as it stands at present one can only say that opinion is divided. However, in addition there is a small colored gentleman in the woodpile here, for the employment of the new chemotherapy may yield very deceptive results. For example, a patient's discharge may cease without mastoid tenderness having ever appeared; the drug will be stopped and he will be discharged,

only to have him come back after some days with a high temperature and signs of serious mastoid involvement. The only remedy I have heard or seen for this state of affairs is to persist in the use of the drug for at least a week after disappearance of symptoms before signing the patient out. The other serious feature of this therapy is that under adequate dosage the clinical picture may indicate improvement while the mastoid bone is being involved with few or no signs or symptoms to indicate it; the otolaryngologists call this "masking." I am sure that Bowers voiced the consensus when he said that in doubtful cases it is well to stop administration of the drug for a while in order to get the true clinical picture.

Mastoiditis.—When a surgical consultant concludes that the mastoid is involved he will usually have had the following points in mind as he made his examinations: (*a*) Tenderness over the antrum from the very beginning is not unusual but it typically stops when good drainage is established; if it continues and grows worse it means serious mastoid disease. (*b*) When mastoid pain begins after the ear has been discharging painlessly for two or three weeks it is indicative of acute mastoiditis; such pain appearing after the discharge has ceased has the same meaning. (*c*) Mastoid pain is usually worse at night. (*d*) A profuse discharge persisting and with pulsation is of serious moment. (*e*) In adults with mastoid involvement there may be little tenderness.

When in the surgeon's opinion operation is indicated every effort should be made to win the family's early consent because delay may endanger life, whereas with an operation performed in time the usual result of the mastoid complication is only to postpone somewhat the ultimate and complete recovery.

Chronic Suppuration.—These cases tax the skill and require all the experience of competent specialists and therefore the general man should not attempt to handle them at all.

PROPHYLAXIS IN THE COMMON COLD

Chilling of any portion of the body and excessive fatigue both no doubt lower resistance to infection and should therefore be avoided, especially during the inclement months. Jarvis (1939) stated the belief that there is a type of individual whose respiratory tract does not adjust well to marked differences in temperature and that such persons should not sleep with the window open in severely cold weather. The crowding together of large numbers of people in closed spaces doubtless facilitates the spread of the common cold and ideally one should shun such crowds, but some fun must be had in life too and man is a gregarious animal. Regarding the more specific methods of prophylaxis the following may be said:

Bacterial Vaccines.—The studies of Hauser and Hauser (1939) at the University of Michigan, of Diehl *et al.* (1938–40) and of Cowan and Diehl (1944) at the University of Minnesota, of Siegel *et al.* (1943) among the personnel of the Visiting Nurse Service of New York City, and of McGee *et al.* (1944) in a large industrial plant, in all of which there were adequate control groups, failed to demonstrate the practical value of "cold" vaccine whether of the orally or subcutaneously administered types; the Council on Pharmacy and Chemistry of the American Medical Association has still not accepted these vaccines.

Vitamins.—The controlled study of Cowan *et al.* (1942) yielded no indication that either large doses of vitamin C alone or large doses of vitamins A, B_1, B_2, C and D and nicotinic acid (niacin) have any important effect on

the number or severity of infections of the upper respiratory tract when administered to young adults who presumably are already on a reasonably adequate diet.

Sulfonamides.—In the United States Navy during War II there was undertaken a program for the control of streptococcic infections and their disabling sequelae through the administration of prophylactic doses of sulfadiazine to about 250,000 naval trainees between December, 1943, and April, 1944; according to Carter (1945) the measure was later instituted at all naval training stations. Coburn (1944), in a preliminary report dealing with observations on only 30,000 men at three camps, stated that a continuous daily dose of 0.5 Gm. of sulfadiazine (affording a mean level of 1.4 mg. per cent in the blood and perhaps 0.8 mg. per cent in secretion of the respiratory tract) was almost 85 per cent effective in preventing implantation of *Streptococcus haemolyticus*. The evidence which Coburn presented also showed that during the period of this trial there was a pronounced decline in the instance of catarrhal fever, which is the category in which the common cold is placed in the Navy Medical Service. It is difficult, however, to understand this decline since the sulfonamides are well known not to be effective against most viruses. One might presume that the ordinary common cold of virus origin did not figure in the study at all but that it included only such colds as were sufficiently complicated by bacterial infection to require dispensary or hospital attention; of course this is only armchair reasoning. But I am sure that it is of the utmost importance to bring to the reader's attention the fact that this was practically a "closed" study in that the drug was administered to *all* personnel; since a comparable state of affairs could not obtain in civilian practice, it seems to me that these findings reported by Coburn do not in the least indicate that the ordinary individual going about his busy life is likely to lower the number of his colds by taking sulfadiazine continuously through the winter.

Propylene Glycol Vapors.—Harris and Stokes (1943) obtained clearcut evidence of the air-borne spread of the causative agent of the common cold through the maintenance of a very low concentration of vaporized propylene glycol in the atmosphere of certain of the wards of a pediatric hospital, other wards not so treated being used as controls. The incidence of colds was greatly reduced by this method of prophylaxis of air-borne cross infection, and it is conceivable that the day may be approaching when it will be economically advisable to establish aerosol prophylaxis of this sort in all hospital wards; but again this is a "closed" method since the individual is protected only while he is in residence in the treated space.

Ultraviolet Irradiation.—Experiments have shown that ultraviolet irradiation of closed spaces is almost equally as effective as the employment of the aerosol above discussed; but it seems that irradiation of hospital wards, barracks, schools, and so on, is not as easily accomplished as is aerosol saturation.

DENGUE

(*Breakbone Fever*)

Dengue is an acute infectious but not contagious disease which occurs endemically and sometimes epidemically in warm countries. Boylon, of Java, first described it in 1779, and the American, Benjamin Rush, in 1780. Graham,

in Beyrouth, Syria, in 1903, first suggested that it is mosquito borne, and Bancroft in Australia, in 1906, whose work was confirmed and extended by Cleland, Bradley and McDonald in the same country in 1916, and by Siler, Hall and Hitchens in the Philippines in 1926, showed it to be transmitted by the yellow fever mosquito, *Aedes aegypti;* later work also convicted *A. albopictus* and upon epidemiological grounds both *A. taeniorhynchus* and *A. scutellaris hebrideus edwards* have become suspect. Ashburn and Craig, in 1907, proved that dengue is caused by a filtrable virus; the patient is infective to the mosquito during six to eight hours before the onset of fever and the first two and a half or three days of the illness, and the mosquito, after an incubation period of eight to eleven days, becomes and remains infective for life. In warmer regions where the climatic conditions favor the breeding of mosquitoes continuously dengue is usually endemic, but it may become epidemic in such regions upon the arrival of large numbers of susceptible individuals; this latter fact was emphasized unforgettably during War II when dengue posed a serious problem for us throughout vast regions of the Pacific area. There are some tropical regions, however, in which the disease occurs only in the form of explosive epidemics at intervals of several years though both the mosquito vector and a susceptible population are constantly present; Simmons (1943), as well as many others, thinks it likely that in these regions a reservoir of the virus is maintained in some lower animal, probably monkeys, in the inter-epidemic period. Dengue has several times been epidemic in the southern United States, the 1922 epidemic having assumed enormous proportions; Levy said that there were 500,000 cases in Texas between June and December. In the Greek epidemic of 1928, there developed 239,000 cases in Athens alone in one month.

There is considerable variability in the severity of the symptoms in outbreaks of dengue and perhaps also some geographic differences in the characteristics of the disease, which has given rise to the description of numerous "new" or "dengue-like" maladies, but in the main the picture is that which follows. After an incubation period varying between three and thirteen days but with an average of about five days, the onset is sudden with severe headache, tenderness of the eyeballs and pain behind them, muscle and joint aches and usually excruciating backache (often much aggravated by movement), extreme prostration, puffiness and redness about the eyes, diffuse redness of the palpebral conjunctiva without lacrimation or photophobia, rapid rise of temperature to 103° to 105° F. (39.5°–40-5° C.) and a pulse rate which though moderately rapid during the first day soon becomes quite markedly slow despite the fever. On the third day the temperature usually falls rapidly and the patient feels much improved; however, usually on the fourth or fifth day, the symptoms return and the fever is frequently higher in this second bout than it was in the first. Sometimes there are third or fourth bouts at intervals of a few days but in other instances the "saddle-back" type of temperature curve is not seen. The acute phase in most instances covers only a period of about seven days; recovery is usually by crisis, often with a sweat, diuresis and nosebleed. In the majority of instances—68 per cent in Cavanagh's (1943) series—there is a pea-sized enlargement and some tenderness of the lymph glands, the posterior cervical glands being the most commonly affected, with the anterior cervical, the epitrochlear, the axillary and the inguinal glands affected in the order named. An unusual phenomenon was observed in 89 of the 318 patients of Kisner and Lisansky (1944) in that they exhibited a

reversed diurnal variation of fever with a higher temperature from 8 A. M. to 2 P. M. than from 2 P. M. to 10 P. M. Two distinct types of rash are seen in dengue. Stewart's (1944) rash "A" is a toxic type which occurs on the third to fifth day and is variable in appearance and quite evanescent. Usually it is a scarlet diffuse redness of the chest and shoulders and upper arms with islands of normal skin half the size of a dime giving the appearance of white spots scattered over the scarlet background. This rash is suggestively measles-like in appearance and may also cause the observer to think of dermatitis medicamentosa in the differential diagnosis. Rash "B" occurred in only about 20 per cent of Stewart's cases but it was seen in 86 per cent of Simmons' (1943) cases. This rash, which appears at or following the termination of the febrile period, gives the appearance of a shower of petechiae; it involves the feet and legs below the knees with perhaps a few spots on the thighs and wrists and occasionally in the roof of the mouth. In some cases the rash is blotchy and erythematous and the petechiae are absent, and sometimes there is itching. The rash fades out in a few days. One of the most constant features of the disease is leukopenia with a "shift to the left" in the granulocytes. Sometimes there is more albumin in the urine than would be expected from the febrile reaction. Loss of appetite is complained of by practically all patients and in some there is nausea and vomiting and abdominal pain. Elek (1944) reported that altered taste was present as an important diagnostic symptom in 86 per cent of 154 patients studied in an endemic area in New Guinea. Almost invariable sequelae of dengue are anorexia, muscular weakness, insomnia, lack of ambition and mental depression, the latter lasting for several weeks.

Apparently the immunity of adult inhabitants of endemic localities results from previous infection, because when the disease is introduced into a new region practically all of the population are attacked and when individuals from dengue-free places move into endemic areas they contract dengue within such a short time that the disease is considered as an acclimatization fever. How long immunity lasts following an attack is not known but many clinicians in dengue regions believe that individuals not uncommonly experience repeated attacks within a few years; however, Simmons (1943), reviewing the evidence, felt that the immunity conferred by an attack probably lasts for a very long time. Nevertheless, McCarthy and Brent (1943) wrote of an area in East Africa in which many of the permanent inhabitants have mild attacks annually; Kisner and Lisansky (1944) described a case in which what seemed to be a second attack occurred approximately two months after the first; and Megaw (1943) stated with assurance that second attacks are relatively common though mild, that third attacks are infrequent, and that some experienced workers believe that fourth attacks rarely or never occur.

THERAPY

Here, as in its kindred affection yellow fever, we have an endemic and epidemic mosquito-borne disease which, in its characteristic symptoms and capacity for debilitating at a stroke large numbers of persons, cries aloud for specific therapy. But in vain. Indeed, because the disease itself is rarely fatal, except through complications in aged and debilitated individuals and in pregnant women, evidence of serious application to a study of its symptomatic treatment is all but lacking in the literature. During the large experience of the disease in our armed forces in War II, the analgesic combination most frequently employed was 10 grains (0.6 Gm.) of acetylsalicylic acid and ½ to

1 grain (30–60 mg.) of codeine sulfate, but occasionally the employment of morphine was necessary. Le Gac and Servant (1939) said that lumbar puncture relieves the severe headache, but this would seem a drastic procedure in a disease of the nature of dengue. Cavanagh (1943) felt that where large amounts of fluid were taken the disease seemed to run a milder course; he found that the sulfonamides had no effect except occasionally to increase the nausea or anorexia. Hyman (1943) found that during convalescence the feeling of tiredness and general lassitude appeared to respond to various mixtures of belladonna and vitamins, at least sufficiently well to warrant a study of this type of therapy under favorable conditions Simmons (1943) said that no one has employed convalescent serum with success.

PROPHYLAXIS

All attempts to protect against the disease through the employment of vaccines, or drugs, have failed. At the present time the screening of the patients and the attempt to eradicate the mosquito vector are the only weapons at our disposal. However, the rigid application of such measures even under far from ideal conditions can be astonishingly successful, as was shown by Zeligs *et al.* (1944), among others, in the Navy during War II.

DIPHTHERIA

Diphtheria is an acute infectious and contagious disease, caused by *Corynebacterium diphtheriae*, which is endemic in larger centers and often becomes epidemic during the winter months. It occurs chiefly in children and is much less often food-borne (milk or milk products) than is scarlet fever. The incubation period is two to five days. In the beginning of the attack the patient is but moderately indisposed, having a little soreness of the throat and slight elevation of temperature. However, the typical membrane soon begins to form in the throat and by the third or fourth day is quite thick and may cover a considerable part of the fauces. Absorption of toxins from the local lesion gives rise to profound constitutional symptoms, and there may be definite degeneration of the heart muscle, kidneys and peripheral nerves. Bronchopneumonia is a complication in nearly all the fatal cases.

Average cases, if properly treated with antitoxin, show a rapid subsidence of severe symptoms and are fully convalescent in seven to ten days. In especially virulent cases, or those not properly treated, the symptoms may gradually increase in intensity to about the sixth day, when there will be considerable obstruction to the nose and throat by the spreading membrane, a massive cervical adenitis and cellulitis, rapid and feeble pulse, and perhaps subnormal temperature. Then coma supervenes upon the profound sepsis and finally death. In that type of the disease in which the membrane first appears in the posterior part of the nasal cavity, and in the laryngeal type where the symptoms are respiratory from the beginning, the prognosis is especially poor. The chief laboratory aid to diagnosis is still the growing of the organisms from the throat in Loeffler's medium, either upon the slant overnight or upon the swab in the physician's pocket in a shorter period of time, but Goldie and Maddock (1943) stated that the use of a tellurite medium simplifies the isolation of the organism from milk.

According to the Babylonian Talmud (352–427 A.D.), the ancient Hebrews so much feared diphtheria that upon the discovery of the first case in a community the *shofar* was blown (for all other contagious diseases it was sounded only after the third case was reported). The classical description was that of Aretaeus the Cappadocian (*circa* 100 A.D.). Aëtius, in the sixth century, mentions paralysis of the palate as a sequel. A number of epidemics of the Middle Ages were described by prelates of the period; during the Renaissance and well up into the eighteenth century the Spaniards and Italians particularly concerned themselves with the description of diphtheria. I believe that the first recorded cases in America occurred in Massachusetts in 1659. To me it seems a strange thing that the diminished liability to the disease after adolescence was apparently not mentioned in the literature before the publication of Heberden's famous *Commentaries* in 1802. Bretonneau gave the disease its present name in 1826, but the laryngeal and pharyngeal types were not recognized as being the same malady until 1880. In 1883–84, Klebs and Loeffler identified and proved the causal relation of the organism. Von Behring developed antitoxin from the laboratory side and Roux from the practical in 1894; the former worker introduced toxin-antitoxin immunization in 1913, and Schick introduced his test in that year also. The present pandemic developed in the middle of the last century and has reached all parts of the world, though it is unquestionably much more severe and probably more prevalent in colder climates, especially the north temperate zone, than in the tropics. A little before the turn of the century a slight decline in incidence set in, but the rate has not fallen generally and in recent years has risen in some parts of Austria, Germany, Scandinavia, Great Britain and Ireland. In these countries there has undoubtedly been an increase in the severity of the disease also, extremely malignant cases occurring so frequently that before the outbreak of War II an attempt was being made with apparent success to determine a definite correlation between the severity of the disease and the type (*gravis*, *mitis*, and *intermedius*) of infecting organism. Malignant cases have occurred only sporadically in the Western Hemisphere, though Wheeler and Morton (1942) pointed out that the epidemic in Halifax was of that type and that the disease had probably been brought to the port by the crew of a Norwegian tanker; Fleming (1944) expressed the opinion that the introduction of the virulent strains will be very heavy when our service men and women return from Europe at the end of War II. Throughout the world as a whole mortality has considerably diminished, however, and it is but a question of time until the newer immunization methods will effect a similar reduction in the world morbidity figures. In the United States in 1942, in 88 representative cities with a total population of 37,309,215, there were only 260 deaths from diphtheria, and in 34 of these cities (including my own city of Milwaukee with a population of approximately 588,000) there were no deaths at all.

THERAPY

Antitoxin Treatment.—Before the discovery of antitoxin the mortality from diphtheria was about 45 per cent; since its use this figure has been gradually reduced, and now varies between 5 and 10 per cent. Its efficiency depends upon the administration of a sufficient dose as soon as possible to prevent the action of the toxin upon the heart and nervous system. If treated with antitoxin within the first twenty-four hours nearly every patient can be saved. Delay of two, three, or four days may mean irreparable injury to vital organs

by the absorbed toxin, which cannot be neutralized by subsequent administration of even enormous doses of antitoxin. The data, taken from Ker (quoted by Zingher), are well displayed in Table 1:

TABLE 1.—RELATION OF MORTALITY IN DIPHTHERIA TO TIME OF ADMINISTRATION OF ANTITOXIN

Day of illness.	Number of patients.	Deaths.	Percentage of mortality.
First	329	5	1.52
Second	2269	77	3.39
Third	2407	165	6.85
Fourth	1612	176	10.91
Fifth	911	136	14.92
Sixth	416	54	12.98
Seventh	320	53	16.56
Later	327	50	15.29
Total	8591	716	8.33

The first injection should be large enough to control the disease. One large dose given early is far more efficacious than the same amount in divided doses. The usual site for subcutaneous injection is the infrascapular region, for intramuscular injection the outer aspect of the thigh about at the junction of its middle and upper thirds. Very sick patients, those who have received antitoxin only after delay, or patients in whom the disease is progressive because of an insufficient first dose, should be given a large intravenous injection whenever feasible. In this way the full value of the antitoxin is obtained at once; the absorption from the subcutaneous injection is so slow that many hours must elapse before any great amount of antitoxin finds its way into the general circulation.

The following table (Table 2) gives the doses recommended by the New York City Department of Health; elsewhere in this and other countries doses twice this size are often given, but it has not been shown that the results are better than with the dosage stated in the table. Horne's (1944) statement that in recent gravis infections in England he had found it necessary to give as high as 500,000 units over a period of several days is certainly a surprising one.

Cases of laryngeal diphtheria, moderate cases seen late at the time of the first injection, and cases of diphtheria occurring as a complication of the exanthemata should be classified and treated as "severe" cases.

In all cases a single dose of the proper amount, as indicated in the schedule, is recommended.

It is recommended that the methods of administration be as follows:

Mild cases: subcutaneous or intramuscular.

Moderate cases: intramuscular or subcutaneous.

Severe cases: intravenous or intramuscular.

Malignant cases: intravenous.

When the antitoxin has been administered early enough and in sufficient dose to be fully effective, a striking improvement is soon seen, as manifested

by a fall in temperature and a favorable change in the character of the cardiac and nervous symptoms. Within twenty-four hours of the injection of the antitoxin the membrane stops spreading, begins to soften and loosen, and the swelling of the mucosa subsides. Zingher wrote: "In some cases the membrane apparently spreads and the alarmed physician is tempted to give a second dose of antitoxin. What has really happened, however, is that the area of mucous membrane which corresponds to the extending portion of false membrane has been injured by the toxin previous to the injection of the antitoxin, and the appearance of the fibrinous exudate is simply the later manifestation of the damage that has already taken place."

TABLE 2.—AMOUNT OF ANTITOXIN REQUIRED IN THE TREATMENT OF DIPHTHERIA

	Mild cases.	Moderate.	Severe.*	Malignant.*
Infants 10 to 30 pounds in weight (under two years).	2,000 units to 3,000 units	3,000 units to 5,000 units	5,000 units to 10,000 units	7,500 units to 10,000 units
Children 30 to 90 pounds in weight (under fifteen years).	3,000 units to 4,000 units	4,000 units to 10,000 units	10,000 units to 15,000 units	10,000 units to 20,000 units
Adults 90 pounds and over in weight.	3,000 units to 5,000 units	5,000 units to 10,000 units	10,000 units to 20,000 units	20,000 units to 40,000 units

* When given intravenously one half the amount stated.

Deleterious Effects of Antitoxin Injections.—In a rather large proportion of cases an urticarial rash with a slight rise in temperature occurs from two to seven days after the injection; rarely other types of rash are seen with more severe constitutional symptoms. Entirely distinct from these slight effects, from which recovery always ensues, are occasionally severe anaphylactic reactions. Park wrote: "A few minutes after an injection about one in every thousand persons develops a rapid and feeble pulse, nausea and a feeling of suffocation. With stimulation and, if necessary, artificial respiration, recovery soon ensues. Those who frequently suffer from attacks of asthma are liable to an attack after an antitoxin injection. There have also been recorded a few deaths. These have occurred chiefly and perhaps wholly in cases of status lymphaticus. About one death has occurred for every 70,000 persons injected, and these deaths, with possibly two exceptions, have followed the first serum injection. The fear of repeating a serum injection because of having sensitized the patient is almost wholly groundless. There need be no fear in giving a second intramuscular or subcutaneous injection to any person who has not suffered severely from the first. The only difference in the effects of the two injections will be that the serum reaction will follow almost immediately the second injection."

An intravenous injection may be followed by a chill and an accompanying rise of temperature lasting about two hours. Osgood has shown that the liability to chill is slightly greater when the antitoxin has been diluted with saline solution before injecting. If a second injection is given intravenously after a considerable lapse of time, it should be given even more slowly than the first.

Patients who have a history of asthma and are suspected of being hypersensitive to horse serum, or who have had antitoxin some time previously, should be given a preliminary intradermal test: a minute amount of the antitoxin diluted 1:10 with sterile salt solution is injected intradermally on the flexor surface of the forearm. Individuals who are unusually susceptible to horse serum will show within twenty minutes, at the site of the test, a large urticarial wheal surrounded by a distinct areola. In these cases administration should proceed as follows, the injections being made at twenty-minute intervals: 0.1 cc. (diluted 1:10) intradermally; 0.1 cc. (diluted 1:10) subcutaneously; 0.5 cc. (diluted 1:10) subcutaneously; 1 cc. (diluted 1:10) subcutaneously; 0.5 cc. (undiluted) intradermally; 0.5 cc. (undiluted) subcutaneously; 0.5 cc. (undiluted) intramuscularly; the remainder in 1 cc. doses (undiluted) intramuscularly.

All of these reactions are becoming less frequent because in the refined and concentrated antitoxins now obtainable the constituents of the serum or plasma other than the antitoxin-bearing globulins have been largely removed. One cubic centimeter of epinephrine hydrochloride, 1:1000 solution, is useful in combating the alarming symptoms.

Dextrose in Severe Cases.—In America it is exceptional for a case of diphtheria not to respond to antitoxin given early and in adequate dosage, but it is common hospital experience to encounter such failures in cases that have come under treatment too late. Abroad, as previously mentioned, cases with overwhelming toxemia from the very beginning are being seen with distressing frequency. In 1930, Schwentker and Noel confirmed the observations of others and added evidence of their own to show that profound changes in carbohydrate metabolism in the human are caused by the toxin in these severe cases—exhaustion of glycogen from the liver and specialized conducting tissue of the heart with a simultaneous rise in blood sugar, sometimes followed by a period of hypoglycemia, then a final hyperglycemia due to toxic depression of the pancreas and other sources of insulin supply. Benn, Hughes and Alstead have shown that, following intravenous injection of dextrose solution in these cases, the delayed return of the blood-sugar curve to normal is comparable to what occurs in diabetes; they reported a series of hypertoxic cases in which the use of dextrose and insulin to supplement antitoxin resulted in a notable reduction in mortality. Begg and Harries (1935), of the same group, confirmed the findings as to the importance of dextrose administration but were not convinced of the value of including the use of insulin, an important conclusion since the injection of insulin without adequate laboratory control might easily result in a hypoglycemic reaction being mistaken for a cerebral complication of the disease. Hoyne (1936) instituted the following routine at the Chicago Municipal Contagious and Cook County Contagious Disease Hospitals with an apparently fine effect upon the death rate:

(*a*) *Selection of Cases.*—Dextrose is given to all patients in any of the following groups: (1) ill more than three days before receiving antitoxin; (2) those having the type of cervical adenitis commonly known as "bull-neck," irrespective of the day in the course of the disease that antitoxin was administered; (3) those with marked albuminuria; (4) all postnasal and all other malignant types of any character.

(*b*) *Dosage.*—Five hundred to 1000 cc. of 10 per cent solution by the gravity method.

(*c*) *Repetition.*—Once daily for at least eight days.

Blood Transfusion.—In an area in Russia in which the gravis type of diphtheria was accompanied by a mortality of 65 per cent despite the use of antitoxin, Sidorov (1943) reported a series of 42 patients in which the mortality rate was only 33 per cent following the use of blood transfusions in addition to antitoxin; the report, however, does not indicate that the series was controlled at all and therefore the findings are open to doubt.

The Sulfonamides.—Fisher (1940) reported the successful treatment of a small series of cases with sulfanilamide, but with such a doughty and venerable specific as antitoxin available it would certainly seem to me unwise to undertake a shift to chemotherapy save perhaps in markedly serum-sensitive individuals. However, it has recently been suggested that in some of the severe cases there may be an associated infection with hemolytic streptococci; under such circumstances one can certainly agree with Fleming (1944) that it might be advisable to employ chemotherapeutic agents along with antitoxin.

Cevitamic Acid.—Since cevitamic acid (vitamin C) may be isolated from the adrenal glands and these glands have long been known to suffer in diphtheria, it has been thought that possibly the administration of large amounts of this vitamin might be worthwhile in severe cases, but Dieckhoff and Schuler (1938) did not find it so from the standpoint of either complications or mortality. Pakter and Schick (1938) also found that cevitamic acid was unable to alter positive Schick tests.

Cardiac Complications.—It is doubtless true that heart failure is today the most common cause of death in diphtheria; *practically all these deaths occur in cases in which antitoxin has been withheld too long or given in too feeble dose.* The usual circulatory stimulants are of little avail here, and because of the degenerative change in the heart muscle digitalis is looked upon as contraindicated. Hoyne believes that the dextrose treatment (see above) has been effective in preventing myocarditis in many instances. Of course the patient must be kept without pillows, fed through a glass tube and not allowed to rise even partially from the supine position for any purpose whatsoever. Pointing out that restlessness is the most important and constant warning sign of increasing obstruction and anoxemia, Neffson and Wishik (1934) counseled against the use of strong sedative drugs; for sedation they gave whiskey, 1 drachm (4 cc.) per year up to ½ ounce (15 cc.), diluted with water, sweetened with sugar and given every three hours.

It is the part of wisdom to continue heart vigilance for several weeks following diphtheria and, even though the patient has to all appearances grown strong, to insist that he return gradually to full physical activity; Burkhardt *et al.* (1938) felt that where possible electrocardiographic studies should be made and complete inactivity be enforced until the electrocardiogram has returned to normal; Wesselhoeft (1941) also advocated an increased routine employment of the electrocardiograph on diphtheria wards.

Local Treatment.—The nose and throat are nowadays left very much alone, though a gargle or spray of saline or Dobell's solution is sometimes employed. Wesselhoeft says that hot glucose irrigation of the throat every three hours greatly reduces the foul odor in a diphtheria ward; if done gently it is apparently very soothing. Many men like to use a steamy inhalant (see Common Cold) for its soothing effect on the mucosa; perhaps it is best here to omit drugs and use just the steam alone. Neffson and Wishik believed the expectorant action of syrup of ipecac may aid in loosening the membrane in severe cases; 10 minims to 1 drachm (0.6–4 cc.), depending upon age, every three hours.

Diet.—If vomiting has supervened, all mouth feeding must cease and sole reliance be placed upon the intravenous administration of dextrose; if much fluid is being lost dissolve the dextrose in Locke's solution instead of water to make up the loss in salts. Many young children refuse all food in the severe cases even if not vomiting; if possible they should be got to take some milk, which may be fortified with cream; or it may be offered in the form of eggnog which is very nourishing. The following eggnog contains no mixture of liquors and only one fourth as much alcohol as the familiar beverage: to the well-beaten yolk of an egg add the following with stirring—½ pint milk, 6 teaspoonfuls brandy and 5 level teaspoonfuls sugar. This should be offered for a few sips at frequent intervals during several hours. The addition of a small amount of nutmeg is pleasing to adults but not always to children; the white of the egg, beaten with a little sugar and placed on top, makes the whole more appealing especially if dusted with nutmeg.

As soon as possible the patient should be placed upon such a diet as that described in Common Cold.

The Period of Quarantine.—The patient should be kept isolated until two successive nose and throat cultures prove negative. Attempts to lessen the length of this period are usually made by the employment of Dobell's solution and other mild antiseptics. If the cultures continue positive for several weeks, guinea pig inoculations should be made to determine the virulence of the organisms. I believe it is now conceded that the use of lactic acid organisms in the spray, or naturally soured milk as a gargle, only hastens the disappearance of the diphtheritic membrane, but does not produce cultures negative to *C. diphtheriae.*

Paralysis.—In general, the various types of paralyses so commonly associated with diphtheria are estimated to occur in from 10 to 25 per cent of all the cases. That of the swallowing muscles which sometimes occurs at the height of a severe case requires nasal or parenteral feeding. Diaphragmatic paralysis is rare and nearly always fatal. The more usual type of postdiphtheritic paralysis, that of the arms or legs, comes on in from one to six or seven weeks and is usually transient. Recovery may be hastened by massage, and some men also feel that the use of strychnine sulfate in tonic doses is justified. As this condition sometimes precedes late cardiac failure the patients should be kept perfectly quiet. Of course antitoxin "big and early" will prevent these paralyses; in those appearing after convalescence is established it is not indicated.

Emergency Relief in Laryngeal Cases.—The dyspnea is caused by one or more of the following: a partially detached membrane which has been drawn down into the lumen of the glottis; obstruction by tenacious mucopurulent secretion; edema of the inflamed subglottic tissues; spasm of the glottis. The measures available for the relief of this very serious condition—removal of membrane with forceps or with an applicator introduced through the laryngoscope; intubation, tracheotomy, aspiration—will not be described here as they are all highly specialized procedures which can only be learned upon the cadaver and in the ward and not from the pages of a book.

The Carrier.—The gamut of antiseptic sprays, gargles, swabs and snuffing powders (including the sulfonamides) has been run and it is now the consensus that simple local cleanliness, best promoted by spraying and gargling with normal saline solution, will accomplish whatever is to be hoped for (which is practically nothing!) from local treatment. Tonsillectomy is said to be often helpful.

PROPHYLAXIS

Who Should Be Immunized and When.—Before the age of six months many babies are protected against diphtheria if their mothers are immune, but fully 95 per cent of children are susceptible when they reach the age of one year, as indicated by the Schick test. From that time on susceptibility slowly declines, as "natural" immunity is slowly acquired, until at the age of seventeen only about 18 per cent are susceptible. Beyond this age susceptibility does not seem to decrease, for from 10 to 20 per cent of adults show a positive Schick reaction (10 per cent in Pygott's [1938] series of recovered individuals showed a positive reaction after six or more weeks). These figures are true only for individuals living in the more crowded cities; in rural sections the percentage of susceptibility is much higher for both children and adults. Zingher stated some years ago that among nurses coming into training schools from small towns and rural sections, the Schick test was positive in 40 to 80 per cent; Wishart (1943) found it positive in about 53 per cent of a group of University of Toronto students. Now, since over 80 per cent of all cases of diphtheria occur in children under the age of ten, and over 64 per cent of all cases and 80 per cent of all deaths occur in children under the age of five, and since almost 100 per cent of children receiving proper prophylactic treatment become immune, the very clear professional duty is to immunize all children as young as possible. In most cities nowadays the public health authorities are assiduously immunizing school children but responsibility for immunizing the even more susceptible group from six months to six years still rests with the general practitioner. The task is somewhat simplified by the fact that the Schick test may be omitted for the reason that these youngsters are practically all susceptible, but the point of just when best to set about the immunization has been a rather delicate one except that there is general agreement that it should take place somewhere between the ages of six months and one year.

Blum has shown that a variable proportion of infants retain the passive immunity inherited from their mothers as long as nine months; therefore, in a group injected before this time some individuals will not be protected because of the inability to graft an active immunity upon a preexisting passive one. From their studies, Greengard and Bernstein (1935) concluded that if immunization is to be carried out at six months preliminary Schick tests should be done and only the positive reactors inoculated, the negatives being retested and the new positives injected when they appear. Otherwise, routine immunization should be withheld until between nine and twelve months, when practically all babies will have lost their passive immunity. These findings accord with the belief of most pediatricians that the best time to inoculate is toward the close of the first year. (For a comprehensive immunization schedule see Smallpox.)

Just before the outbreak of War II, France became the first major nation to make diphtheria immunization compulsory.

Preparations Available.—The first standardized preparation used was the toxin-antitoxin of von Behring, a diphtheria toxin neutralized by antitoxin so that the toxic properties were lost but the antigenic properties remained. It was highly effective but had to be given three times at intervals of a week and there was always some slight danger of serum sensitization with it because of the small amount of horse serum it contained. Severe local and general reactions were fairly frequent in older children and adults and the product was relatively unstable and therefore always had to be used as fresh as possible.

This preparation was almost entirely replaced throughout the world by the toxoid developed by Ramon, a diphtheria toxin modified by the addition of 3 to 4 per cent of commercial solution of formaldehyde and incubated at from 38° to 40° C. for four to six weeks; like toxin-antitoxin it has lost its toxicity but retained its antigenic properties. Some local and general reactions to this toxoid occur (see below), but it contains no horse or other serum and therefore cannot cause serum sensitization and its effectiveness is considered to be much higher than that of toxin-antitoxin. The next product to be given extensive practical trial was alum-precipitated toxoid, which resulted from the work of Glenny and Havens and their associates and was developed clinically principally by Graham, Murphree and Gill; Baker and Gill; Saunders; McGinnes, Stebbins and Hart; and Keller and Leathers. It is a toxoid whose rate of absorption has been slowed by precipitation with alum, the advantage of this lying in the fact that less antigen is lost by excretion and therefore complete immunization might theoretically be accomplished with one injection. The incidence of local and general reactions (see below) is less than with toxoid and serum sensitization is no more to be feared with it than with toxoid.

During the years in which this immunization work has been developing, trials have been made of mixtures made with goat and sheep serum but these preparations have been outmoded by the newer ones. The toxin-sodium ricinoleate method of Larsen and the percutaneous method of Lowenstein have not won places for themselves. The method of Jensen (1937), in which a single injection of toxoid is followed by nasal instillations of the same agent, has not had extensive trial.

Alum-precipitated Toxoid.—This preparation is injected subcutaneously at the deltoid insertion in a dose of 0.5 or 1 cc., depending upon which manufacturer's product is being used. According to Stebbins (1943), the Diphtheria Sub-Committee of the Committee on Administrative Practice of the American Public Health Association recommends that two doses should be given children under school age, with an interval of one month between. Being an insoluble substance this preparation raises a firm nodule at the site of injection and around it there appears and persists for a few days a trifling inflammatory reaction, the nodule becoming smaller as the material is absorbed and disappearing completely in six weeks. Very rarely—practically never in children under two years of age—there may be more marked local redness and swelling and discomfort and sometimes malaise, anorexia, aching and a slight fever. But these reactions occur so seldom up to six or eight years of age that the possibility is usually disregarded as being of no moment except in individuals known to be definitely allergic. Occasionally there occurs a sterile abscess at the site of injection, doubtless a tissue reaction to the sterile insoluble foreign body; but this is a very rare occurrence indeed in young children.

Toxoid (Anatoxin).—This preparation is injected subcutaneously in a dose of 1 cc. According to Stebbins (1943), the Diphtheria Sub-Committee of the Committee on Administrative Practice of the American Public Health Association recommends that for children under school age three doses be given at intervals of one month. General reactions are rare in children under eight years of age and in this group local reactions of any moment occur very infrequently, but in older children and adults the incidence of both types considerably increases. An intracutaneous test dose of 0.1 cc. of toxoid diluted with salt solution (1 in 20) is sometimes given and the toxoid then withheld from those who show a positive skin reaction (a flush of 10 mm. or more in

diameter, with perhaps some slight swelling, after forty-eight hours—Moloney test); such skin-test solutions are distributed with some of the commercial preparations. Experience has shown that unduly severe reactions in adults may be avoided if the regular doses are preceded by two preliminary doses of 0.1 and 0.25 cc. of the undiluted toxoid at an interval of one week.

Choice of Preparations.—A few years ago alum-precipitated toxoid seemed to be preferred by most workers in the United States and England, but in Canada the use of toxoid was always persisted in and there was insistence on the full course of three injections (Fitzgerald *et al.*, 1938; Benjamin *et al.*, 1938). In the United States, Bundesen (1939) and his associates of the Chicago Board of Health also pronounced in favor of a return to the three doses of toxoid at intervals of a month; their comparative studies employed large numbers of children and extended over several years. In a more limited study in New Haven, Hillman and Linde (1939) likewise found three-dose toxoid the most effective method. It is my impression that for diphtheria immunization alone a swing back to toxoid has set in rather generally throughout the United States but that most pediatricians nowadays are preferring the two-dose combined alum-precipitated diphtheria and tetanus toxoids (see article on Tetanus and the comprehensive immunization schedule in Smallpox).

Rapidity of Immunization.—It is now considered that with either the toxoid or alum-precipitated toxoid methods antitoxin begins to appear in the blood in a few days and full immunity is reached in 95 per cent or more children in four to six weeks.

Reimmunization.—Ideally all individuals should be Schick tested three to six months after immunization; the positives can then be reimmunized with reasonable assurance of success by either method. Preliminary desensitization had perhaps best precede the second trial. Fischer *et al.* (1940) pointed out that children tested during the febrile period of an acute infectious disease in whom bullous Schick reactions develop should be retested some time after recovery before being considered susceptible to diphtheria.

Duration of Immunity.—A number of men are now urging that upon entrance into school the child be given another injection since Schick negativity several years after the original immunization does not always mean complete protection, the antitoxin content per cubic centimeter of blood (1/25 unit) now held necessary for such protection being much more than the minimum content (1/250) to insure Schick negativity in most instances. And even Schick negativity is not retained by all children to school age; Schwartz and Janney (1938), retesting 145 children six or seven years after immunizing them with 3 doses of toxoid, found that 22 per cent had reverted to a Schick positive test. Benjamin *et al.* (1940) found 14.9 per cent of their larger series positive after five to eleven years, which was twice the proportion positive after four to five years. Duke and Stott (1943), in a rural area in England in which 95 per cent of the children had been immunized, found the proportion who had lost their immunity rose steadily from 4 per cent after two years to 18 per cent after six years. In London, Freeman (1942) found over four fifths of 2425 children at school-entry age Schick-positive. Reimmunization with one injection upon reaching the school age of five or six years seems a decidedly sound procedure.

Tonsillectomy and Immunity.—Buice's (1934) study I think convincingly indicated that tonsillectomy neither decreases the incidence of diphtheria nor increases Schick negative immunity.

Prophylaxis with Antitoxin in Nonimmune Exposed Cases.—Formerly it was the routine practice to give an immunizing dose of antitoxin to children who had been exposed to diphtheria and who had not been immunized. Nowadays, it is more customary to wait a while, watching the child carefully for the early signs of the disease and then giving a suitable therapeutic dose of antitoxin should they appear. This change of policy has followed the repeated observation that even a small dose of the serum may cause an alarming reaction or render the patient sensitive to a therapeutic dose subsequently administered. Of course if the child cannot be watched, it should be given 1000 units of ordinary treatment antitoxin as soon as possible; this establishes an immediate passive immunity which lasts for about three weeks.

Combined Diphtheria and Tetanus Toxoids.—See article on Tetanus.

Combined Diphtheria and Pertussis Immunization.—See article on Whooping Cough.

Order of Immunization Against Diphtheria and Other Acute Infectious Diseases.—See article on Smallpox.

DYSENTERY

Nearly all the notable writers since that able Byzantine compiler, Alexander of Tralles (525–605 A.D.), have left accounts of dysentery. During the Thirty Years' War in the seventeenth century it ravaged the Continent and England, where the great Sydenham among others described it. The disease continued widely prevalent throughout the eighteenth century in Europe, and following Clive's victorious campaigns the varieties encountered by British medical officers in India began to be described. The etiologic agents of bacillary dysentery were discovered by the following workers: Shiga in Japan (1898), Kruse in Germany (1900), Flexner in America (1900), Strong and Musgrave in the Philippines (1900), and the Y-bacillus by Hiss and Russell in America (1903). Lambl probably saw the causative ameba of the protozoan type of the disease in 1860 when he discovered *Giardia intestinalis*, but the definite differentiation between epidemic bacillary dysentery and endemic amebic dysentery was made by Koch (1883) and Kartulis (1886–1891) in Egypt.

AMEBIC TYPE
(*Amebiasis*)

Amebiasis is an infectious disease caused by *Endamoeba histolytica*. The organism causes more or less extensive areas of ulceration throughout the large bowel, giving rise to the symptom-complex of amebic dysentery; entering the blood stream it is also sometimes carried to the liver, very rarely to the brain, in either of which sites it may cause serious abscess. By extension, lung involvement sometimes occurs, and indeed pulmonary amebiasis without a "primary" liver abscess and liver abscess without antecedent dysentery are not unknown, but that the organism frequently spreads all over the body and infects many organs is certainly not proved; I have seen one report of a perinephritic amebic abscess and two reports of amebic infection of the uterus. Ulcers of the skin may occur after surgical drainage of an amebic abscess or in the anal and penile regions by direct extension from the rectum. Amebiasis is acquired by ingestion of the encysted form of the organism which has been passed from the

bowel not of an acutely ill patient but one who is convalescent or is a chronic carrier of the cysts; thus it may be propagated by fecal pollution of garden truck or of food during its handling or its exposure to flies, or by the drinking of feces-polluted water, or by direct contact between individuals as seems sometimes to be the case in prison and asylum epidemics. It usually begins gradually, after an incubation period of roughly seven to seventy-seven days (Chicago epidemic of 1933), with intermittent attacks of bloody, mucoid diarrhea, without nausea, loss of appetite, or fever, and with only moderate tenesmus and abdominal pain; occasionally, however, the attack is fulminating and of the acute appendicitis type, and in "chronic appendicitis" this disease should be thought of also. In some instances secondary bacterial invasion of the bowel occurs, the patient becomes anemic and emaciated, and in a few years is exhausted out of life, but an outstanding characteristic of the disease in the vast majority of cases is its chronic and intermittent course. Granulomas of the lower bowel, resembling carcinoma in many respects, have been reported a number of times. The laboratory diagnosis of amebiasis requires special knowledge and skill; the roentgen appearance of the colon will not alone establish the diagnosis. A complement fixation test is in process of development but is still looked upon, according to Rees *et al.* (1942), of the U.S.P.H.S., as of adjunctive rather than of primary value in diagnosis.

Since amebiasis is well known to exist in tropical and subtropical countries it has been commonly thought to occur only in these regions, but many studies in recent years have shown that it is endemic in the temperate zones as well. The cases usually occur sporadically, though several in a single family is a common finding; only rarely does the disease become briefly epidemic and these epidemics do not show seasonal preference. Infants and children as well as adults may be affected. Craig's "very conservative" estimate is that between 5 and 10 per cent of the people in the United States are infected with *E. histolytica*; Faust (1942) felt that possibly 20 per cent would be a more nearly accurate figure, but Hood (1943) found an incidence of only 7.9 per cent in the 2000 patients and employees of a hospital in Chicago, the study extending over a twelve-year period which included the epidemic years in that city. Faust (1941) recovered the organism from the bowel in 6.44 per cent of 202 autopsies performed within four hours after accidental death in New Orleans. It is not unlikely that the incidence of amebiasis will increase in the United States after the conclusion of War II because many of our soldiers will return from tropical regions where the disease is very prevalent.

Therapy

In what follows, the "specific" drugs are individually considered and then there is presented a chart (Table 3) offering several alternative plans for their use. The reader will please understand that this chart does not represent the practice of any single eminent individual or clinical group but has merely been put together by me in the belief that some attempt at standardization is required if the man treating an occasional case of amebiasis is to make the best use of the considerable amount of information now available. The essence of that information is that for success the organisms must be vigorously assailed by several agents and that it has to be done very carefully and cautiously—it is this which I have sought to get into the chart. Then follow discussions of diet, general and nursing care, the complications, prophylaxis and the carrier.

TABLE 3.—SEVERAL ALTERNATIVE PLANS FOR THE TREATMENT OF AMEBIASIS WITH SPECIFIC DRUGS (THE DOSES ARE FOR ADULTS)

First course of treatment.		Second course (To begin after ten days' rest).	Third course (After ten days' rest).
Emetine hydrochloride (subcutaneously or intramuscularly). A total dose not to exceed $\frac{1}{6}$ grain per 2.2 lbs. body weight (10 mg. per Kg.). Give two thirds of the total amount in first six days, remaining one third in second six days. (If not a case of moderate or considerable severity, the emetine may be omitted).		Bismuth subcarbonate (or subnitrate), three drachms (12.0 Gm.) in milk or water three to five times daily.	Bismuth salt may be continued as long as patient can take it.
At the same time give any one of the following:		At the same time any one of the following depending upon which plan is being pursued:	
PLAN A	Carbarsone, 4 grains (0.25 Gm.) twice daily by mouth for ten days.	Diodoquin, 3 tablets of $3\frac{1}{3}$ grain (0.21 Gm.) three times daily for twenty days. (Or chiniofon, 16 grains (1 Gm.), three times daily by mouth for eight days; or try the chiniofon enemas, see Plan D, 1st course).	Repeat the carbarsone course by mouth or try the carbarsone enemas.
PLAN B	Diodoquin, 3 tablets of $3\frac{1}{3}$ grain (0.21 Gm.) three times daily for twenty days. (Or chiniofon, 16 grains (1 Gm.) three times daily for eight days).	Carbarsone, 4 grains (0.25 Gm.) twice daily by mouth for ten days. (Or carbarsone enemas, see Plan C 1st course).	Repeat either the diodoquin or chiniofon course by mouth or try the chiniofon enemas.
PLAN C	Carbarsone, 200 cc. of 1 per cent in 2 per cent sodium bicarbonate solution by rectum, repeating on alternate evenings until at least five enemas have been retained over night.	Diodoquin, 3 tablets of $3\frac{1}{3}$ grain (0.21 Gm.) three times daily for twenty days. (Or chiniofon, 16 grains (1 Gm.) three times daily by mouth for eight days; or try the chiniofon enemas, see Plan D, 1st course).	Repeat carbarsone enemas or try carbarsone by mouth.
PLAN D	Chiniofon, 300 cc. of 2.5 per cent by rectum, to be retained as long as possible; repeated daily for ten days.	Carbarsone, 4 grains (0.25 Gm.) twice daily by mouth for ten days. (Or carbarsone enemas, see Plan C, 1st course.)	Repeat chiniofon enemas or try chiniofon or diodoquin by mouth.

It is unlikely that the courses will have been pursued with only ten-day intervals, but even if they have, then ten days after completion of the third course it will be safe to repeat the emetine provided the patient experienced no reactions during the first course with this drug; thereafter the courses may be given all over again or merely continued without the second trial of emetine. Or it may be advisable at this time to try one of the other drugs or special methods of administration described in the body of the text. Of course the arsenicals and oxyquinolines do not *have* to be alternated in the above definite fashion, for either of them may be given safely in several consecutive courses provided there are intervals of at least ten days between and the physician is ever watchful for evidences of toxic action.

IPECACUANHA AND DERIVATIVES

Emetine.—There are few diseases which respond so quickly to any therapy as does amebiasis to emetine, which was introduced by Rogers in India in 1912, but it is now the consensus that it should be used only to accomplish rapid subsidence of symptoms in moderate to severe cases. The drug's limitations are that it is acutely poisonous if given in fully "effective" doses and that even in much reduced dosage cumulative poisoning may occur if short courses of its use are not separated by periods of six to eight weeks in which the drug is not given; furthermore, the ameba very likely becomes emetine-fast just as the spirochete becomes arsenic-fast. The dictum has been pronounced (Anderson and Leake, 1930) that dosage should be based on weight and should not exceed 1 mg. (1/60 grain) per kilogram (2.2 pounds) for a single dose or a total dosage of 10 mg. per kilogram ($\frac{1}{6}$ grain per 2.2 pounds). The practical administration would work out as follows, using emetine hydrochloride:

60 Kg. (132 pounds) at 10 mg. per Kg. = 0.6 Gm. (10 grains) total dose.
Give two thirds of this total amount in the first six days and the remainder in the succeeding six days:
1 injection of 1 grain (0.06 Gm.) daily for six days = 6 grains (0.36 Gm.).
1 injection of $\frac{1}{2}$ grain (0.03 Gm.) daily for six days = 3 grains (0.18 Gm.).

The patient has then received 9 grains (0.54 Gm.), which is sufficiently close to the theoretical limit for his size. He is not to receive emetine again, if at all, under six or preferably eight weeks, but during this period other drugs may be given.

Subcutaneous injection is not infrequently followed by pain and discoloration of the skin and very rarely even by slough, but it continues to be almost the routine method. Manson-Bahr (1940) said that fewer sequelae occur if the skin is pinched up and the drug injected deeply subcutaneously. Intramuscular injection deep into the gluteal region causes no discoloration, is no more painful and if retraction of the plunger has failed to draw blood up into the syringe one can be sure of not being in a vein; even so, absorption is undoubtedly faster by this route which probably causes many men to hesitate to employ it. It has been said that the injections may be rendered painless by using a 1 to 2 per cent procaine hydrochloride solution as solvent for the drug; it would seem that toxic effects need not be feared from such a practice except in individuals hypersensitive to procaine. Emetine is said to cause very great pain when introduced in enema form; intravenous administration is regarded almost universally as unnecessarily dangerous, though Heilig and Visveswar (1943), in India, did not hesitate to introduce the drug by this route in a rather large series of cases.

Neither auremetine nor emetine periodide has made a place for itself. Emetine bismuth iodide (containing 20 per cent of emetine), which may be given by mouth, is sometimes substituted for emetine hydrochloride; for the adult, 1 capsule of 1 grain (0.06 Gm.) three times daily for four to ten days is about as much as will be tolerated and even this dosage is usually followed by so much nausea and vomiting as to cause its early abandonment—nevertheless, Manson-Bahr still prefers this drug and is dissatisfied unless there is nausea and vomiting to indicate that it is being absorbed.

Toxicity.—Before emetine dosage was placed on a scientific basis we knew

that it frequently caused an increase in diarrhea many times accompanied by nausea; also there were sometimes caused rapidity, irregularity and weakness of the heart beat, changes in the skin and nails, asthenia, neuritis (myositis) and palsy; Manson-Bahr (1941) cited a case in which progressive wasting and eventually a state resembling progressive muscular atrophy was thought to have been due to the use of the drug. Some deaths, apparently in auricular fibrillation, have been reported. Some of these cases were undoubtedly instances of idiosyncrasy to the drug and many others were due to the use of greatly excessive dosage. Brown (1935), reviewing the 554 cases of the Mayo Clinic in which emetine had been used within the limits of our present dosage scheme, found only three reactions in the series. Nevertheless, Hardgrove and Smith (1943), in Panama, observed electrocardiographic changes in 38 of 72 patients receiving emetine, and in the series of Heilig and Visveswar (1943), in India, 9 of the 11 patients with initial normal cardiograms showed some deterioration; strangely enough, in this latter series improvement was shown by a high percentage of patients with previously pathological tracings. It would certainly seem that, considering the high usefulness of the drug, its employment is not unduly dangerous if one keeps the patient in bed and is watchful. Pregnancy, as well as cardiovascular disease, are considered to contraindicate the use of emetine. The chances of myocardial injury probably increase above the age of sixty; in infants emetine is not usually employed.

Ipecac.—The use of sufficient powdered ipecac by mouth for effective amebicidal action is precluded because of the violent vomiting which is caused.

Salol-coated pills have not been uniformly satisfactory; still, as recently as 1934, Simon stated that he resorts to these pills in patients who have resisted the other drugs—50 to 100 grains (3–6 Gm.) at 9:30 P.M. This drastic treatment he felt to be often completely effective.

A retention enema of ipecac is sometimes resorted to. Lawson's method is to place 60 to 120 grains (4–8 Gm.) of powdered ipecac in 1½ pints (750 cc.) of water which is kept hot (but not boiling) for an hour. Then when it has cooled to body temperature the whole preparation, without filtering, is introduced slowly into the rectum (previously washed out with warm water) to be retained as long as possible. Pain and tenesmus cause reduction in the volume of the enema.

Andresen has employed a transduodenal method of introducing the ipecac. Passing the Jutte tube well down into the duodenum in the morning after a twelve-hour fast, or the night before where there is much pylorospasm, the pylorus is encouraged to close by causing the patient to drink 4 or 5 ounces (120 or 150 cc.) of cold milk alongside the tube. Then a pint (500 cc.) of 10 per cent aqueous solution of sodium and magnesium sulfate is allowed to run slowly into the tube at 105° F. (41° C.), usually producing a copious watery evacuation in twenty to thirty minutes and, it is believed, cleaning out the ulcer bases. Twenty minutes after giving the salt solution, 1 drachm (4 Gm.) of powdered ipecac in warm water is introduced and the tube washed with another 50 cc. of water, waiting thereafter an hour before removing the tube to prevent ipecac entering the stomach and causing vomiting. One and one-half to two hours after giving the ipecac frequent feedings are resumed. Seven daily treatments are given, then a week's rest and then another week of treatment. During the second week, when no treatment is being given, the patient is usually constipated and is felt to require soothing laxatives.

ORGANIC ARSENICALS

Carbarsone.—This drug has been found to be vastly superior to treparsol, acetarsone (stovarsol), or any of the other arsenicals and the use of it alone will therefore be discussed in this category. Hauer (1943) described the successful use in German troops during War II of a compound which contained about twice as much bismuth as arsenic; it will be interesting to receive a full report on this drug after the war.

Reed (1934), who was one of the early advocates of carbarsone, advised a total dosage of 75 mg. ($1\frac{1}{4}$ grains per kilogram, 2.2 pounds) body weight to be spread over ten days with 2 or 3 doses daily. The top dose for an adult, if we use 60 Kg. (132 pounds) as the upper limit of weight to be used in calculating (as with emetine), would accordingly be 4 grains (0.25 Gm.) twice daily for ten days. Given in capsules after eating, this dose has been used in a great many individuals with perhaps better success than attends the use of any other drug save emetine; but considering that carbarsone can be used in two or three or even more successive courses with rest periods of only ten days between—a thing wholly impossible with emetine in the light of newer knowledge—it has seriously challenged the eminent position of the classical drug. Some men are cautiously using larger dosage than the above but there is general recognition that this is probably justified only in recalcitrant cases. Mateer *et al.* (1940) said that in their experience at the Mayo Clinic cure was obtained in all but 10 per cent of cases with the smaller dosage, but that they could reduce the number of failures to 3 per cent by giving in addition a chiniofon retention enema (see method under Chiniofon) every other morning during the ten-day period; Schulze and Ruffin (1942) also liked the carbarsone-chiniofon enema combination.

Carbarsone may also be satisfactorily used by rectum. A cleansing soda enema is followed in one hour by instillation into the rectum of 200 cc. of warm 2 per cent sodium bicarbonate solution containing 1 per cent carbarsone, 3 grains (0.2 Gm.) of sodium amytal having been previously given by mouth to insure sleep and facilitate retention of the enema. If the enema is expelled before morning the treatment is repeated on alternate evenings until at least five enemas have been retained over night. Such a course may replace, but should not be given at the same time as, a course of the drug by mouth.

Upon the whole this drug seems to be relatively nontoxic, as indeed one would think it should be for the reason that it was not introduced into practical therapeutics until its safe dosage range had been worked out in animals (an advantage only recently enjoyed by emetine!). Leake pointed out that the similarity of its chemical arrangement to that of tryparsamide might lead us to expect some injuries to the optic tract as the drug comes into more extensive use, but so far the only report has been of a moderate papillitis and retinal edema in a case of Smithies (1934); Reed saw no such injuries in his 400 cases. Smithies' patient also had puffiness of the eyelids and face and albuminuria with granular casts; another patient had laryngeal and pulmonary edema, sore throat, sneezing and lacrimation; and another developed exfoliative dermatitis limited to the hands and arms. Epstein (1936) reported the case of a patient who died from arsenical exfoliative dermatitis apparently induced by doses of the drug within the therapeutic range; autopsy revealed acute fatty degeneration of the liver, which gives point to Reed's (1934) recommendation of the use of liver function tests before prescribing carbarsone. The drug should be withdrawn in patients who experience gastro-intestinal irritation, congestion

of the respiratory tract, visual disturbances, jaundice, neuritis, pruritus, or skin eruptions; frequent examinations should be made to detect enlargement of the liver or spleen or evidences of renal damage.

OXYQUINOLINE DERIVATIVES

It is said that the amebacidal action of the drugs of this group is due to the iodine which they contain; this being the case, one might expect that diodoquin, which is said to contain about 64 per cent of iodine, would be the most effective, vioform with about 42 per cent the next, and chiniofon with about 29 per cent the last. As a matter of fact, however, there is not to be found in the literature a satisfactory large scale comparative study of these three agents.

Diodoquin.—This drug, the newest of the three, seems to be only slightly toxic despite its high iodine content. Silverman (1937), Hummel (1939) and D'Antoni (1943) each reported its satisfactory use in a fairly large series of cases. Of D'Antoni's 84 patients, 81 were cured, 2 of the recalcitrant cases being complicated by a Shigella infection. D'Antoni gave three tablets of $3\frac{1}{5}$ grain (0.21 Gm.) three times daily to adults for twenty days; four children aged six to eleven years received two thirds of this dosage.

Chiniofon (Yatren, Anayodin).—This, the oldest of the three drugs of the group, has been employed quite extensively in the tropics. In the continental United States, O'Connor and Hulse (1935) have perhaps had the largest experience with it; their series comprised 152 cases and upon the whole the results were very satisfactory. To adults they gave 4 pills of 4 grains (0.25 Gm.) each three times daily with meals for eight days; in some instances the diarrhea was increased and there was a scalding sensation during defecation, necessitating reduction to 3 or 2 pills per dose, but treatment was always continued until the full course of 96 pills had been given. Faust (1943) also referred to this diarrhea, but O'Connor and Hulse observed no other toxic symptoms during or following the treatment nor did they know of any in the experience of their colleagues who used the drug. Fatalities have been reported following the intravenous administration of chiniofon, but they are of no significance in the present connection.

Chiniofon may also be given by rectum. Willoughby and Aslett (1931) reported the very successful treatment of 150 cases, giving 10 ounces (300 cc.) of 2.5 per cent solution of the drug preceded by one hour by a 1-pint (500 cc.) enema of 2 per cent sodium bicarbonate solution; the chiniofon enema is retained as long as possible, the procedure being repeated daily for ten days. It is best not to give the drug by rectum and by mouth at the same time. Mateer *et al.* (1940) gave a cleansing saline enema and then introduced the chiniofon solution with the patient in the knee-chest position; after five minutes the following positions are taken in succession, each being held for thirty minutes: right side, back, left side, back. At the outset of the treatment, paregoric is given at frequent intervals if necessary to ensure retention of the enema.

Manson-Bahr's (1941) preferred treatment is the simultaneous administration of chiniofon by rectum and emetine bismuth iodide by mouth.

Vioform.—This drug differs from chiniofon in containing chlorine and, as above stated, considerably more iodine. It is nowadays principally given in the form of enteric-coated capsules, 8 grains (0.5 Gm) being given twice daily for ten days and the course being repeated as often as needed with ten-day intervals. In Anderson and Reed's (1934) group of 60 patients, 1 experienced

palpitation, dyspnea, and a sense of fulness in the head and headache upon taking the drug; there were also some gastro-intestinal symptoms but these have been largely avoided by the use of the enteric-coated capsules that have been more recently developed. Manson-Bahr (1941) was not favorably impressed with vioform in chronic cases. This drug is not used rectally.

MISCELLANEOUS DRUGS

Bismuth Subnitrate (or Subcarbonate?).—James and the late Dr. Deeks, ofthe United Fruit Company Medical Service, have long advocated large doses of bismuth subnitrate in conjunction with other therapy—a heaping teaspoonful well mixed with milk or water three to five times daily. Or some such preparation as that in the prescription below might be used. Others have also found this a very satisfactory adjuvant medication but the recent tendency has been to substitute the subcarbonate salt because of the frequent secondary bacterial colitis thought to make conditions ideal for the occurrence of nitrite poisoning; however, James (1934) deprecated this since he early found the subcarbonate not to be so effective as the subnitrate.

℞	Bismuth subcarbonate	℥vj	180.0
	Sodium bicarbonate	℥j	30.0
	Mix and divide into 30 powder papers (blue).		
	Tartaric acid	℥j	30.0
	Divide into 30 powder papers (white).		
	Label: Stir contents of 2 blue papers in half glass of water; dissolve contents of 2 white papers in separate half glass of water; mix the two and drink while effervescing.		

Shattuck (1939) thought that a preliminary purge with castor oil, bed rest and a generous but strict milk diet are important adjuncts of this bismuth treatment.

Soper (1934) found that when secondary ulcers develop just above the internal sphincter, as in most of the "carriers" of his experience, the powder-insufflation method (using equal parts of bismuth subcarbonate and calomel through a powder blower) is of great value.

Chaparro Amargoso (and Castamargina).—The merits of chaparro as an amebacide were advanced by Nixon many years ago. The whole plant is boiled in water for thirty to sixty minutes and 6 to 8 ounces (180–240 cc.) of the infusion, which should have the color of weak tea, are given by mouth before meals and on retiring; it may also be introduced once or twice daily as a retention enema. While in Mexico City in 1934 I found that a solution of castamargina, the active glucosidal principle which has been isolated there, was being employed as an interval drug between courses of more drastic therapy. Manson-Bahr (1941) said that in the three cases in which he tried chaparro amargoso as a retention enema the results were inconclusive. It seems to me unlikely that this drug will compete successfully with the previously described agents; I am unaware of any thorough modern study of it.

Oil of Chenopodium.—Two cubic centimeters of this drug are given together with 1½ ounces of castor oil at a single dose. Or the oil may be emulsified with acacia and administered by rectum, the anal mucosa being protected with petrolatum and the injection being terminated with 2 ounces of inert oil. The buttocks should be elevated, the enema given slowly and with great care, the first dose not exceeding 8 ounces in the adult; it is to be retained for an hour if possible.

Barnes and Cort reported a series of cases from Siam in which the results were as good as those obtained by the use of emetine. In working among native populations, the two oils already combined can be sent to distant patients who could not otherwise be reached effectively. A point to be remembered is that oil of chenopodium should not be repeated in full dose in less than two or three weeks because of the possibility of renal irritation.

Quinine.—Quinine has been used for a long time for rectal irrigations with more or less success, but the treatments are often very painful. One or 2 liters of 1:2500 to 1:1000 aqueous solution of the sulfate are employed. Quite severe cinchonism not infrequently follows its use by this route. Brooke has employed quinine sulfate satisfactorily by mouth, giving 20 to 30 grains (1.2–2.0 Gm.) daily for six days and repeating after an interval of a week.

Salicylic Acid.—This drug is used in the form of a 2 per cent solution of sodium salicylate by rectal enema. Lutsch, in Africa, extolled the method for the prompt relief of pain and tenesmus. He gave 5 grains (0.3 Gm.) of calomel and allowed nothing but barley water the first day and later a little boiled milk. The enema, to be retained for half an hour, was given six hours after the dose of calomel and repeated on the second and fourth or third and fifth days. For a child a year old 90 cc. of the solution was given and for an adult about 650 cc.

Copper Sulfate.—The De Rivas treatment in use in several tropical countries (Hemenway, 1934; Beregoff, 1935; De Rivas, 1938) consists in the use of hot rectal irrigations of copper sulfate solution given through a stomach tube inserted into the rectum and connected by a glass y-tube to the enema vessel and a waste pail. As the tube is slowly inserted sufficient fluid is admitted to balloon out the intestine so that the tube may be pushed up into the ascending and transverse colon; then a rectal thermometer is inserted. From 1 to 2 liters of a 1:5000 copper sulfate solution at 52° to 55° C. (125° to 131° F.), with 1 ounce (30 cc.) of glycerin per liter, are allowed to flow into the colon at 150 cc. a minute. When there is pain the enema tube is clamped off, that to the pail opened and some of the solution allowed to flow out; after this the treatment is continued and at the close the patient holds the fluid as long as possible. The treatments are given three times weekly for two months and then once weekly for a month. The patient lies on the right side with hips elevated and is prepared by a saline cathartic at bedtime and a cleansing enema in the morning.

Oxygen.—The intestinal oxygenation method of Felsen has been successfully employed by him, Golob (1936) and others; it is described under Ulcerative Colitis.

Phenothiazine.—During War II, Rhoads (1944) reported the successful treatment of his own case of amebiasis which had resisted all of the usual amebacidal agents by the employment of retention enemas of phenothiazine. He used 12 Gm. of phenothiazine suspended in 750 cc. of water at night, following a cleansing water enema. Three treatments on alternate nights apparently eliminated the parasites. Faust (1943) said that a reduction of carbohydrates and an increase in readily digestible animal protein would be justified upon the basis of experimental study.

DIET, GENERAL AND NURSING CARE

In the severe cases, with fever and prostration, the patient must be in bed of course and should receive frequent feedings—every two and one-half hours,

according to Reed—of boiled milk, stale or toasted white bread, white rice, soft cooked eggs, gelatins and tea. Adequate rest may be secured by use of one of the barbiturates (see Insomnia). If there is excessive frequency of bowel movements bismuth should be employed at once and paregoric may be given in 2-drachm (8 Gm.) doses at two-hour intervals to control colic. Occasionally it will be necessary to give a hypodermic injection of ⅛ grain (0.008 Gm.) morphine sulfate, or 1/32 grain (0.002 Gm.) dilaudid, with 1/120 grain (0.0005 Gm.) atropine sulfate. Should a period of costiveness then succeed the diarrhea there is no harm in giving a cathartic. Tenesmus may accompany rectal ulceration; the following might be useful, as suggested by Fantus:

℞	Iodoform	ʒiiss	10.0
	Olive oil	℥iv	120.0

Keep on ice. Inject 1 tablespoonful into rectum every four to six hours.

After the disappearance of acute symptoms in the fulminating cases there is no need to keep the patient in bed; indeed, in average cases without prostration or fever he need never have been put to bed—*except during the period of emetine therapy, when experience dictates caution because of the cardiotoxic nature of the drug.* In building up the diet one should bear in mind that this patient will require smoothness combined with high protein and low carbohydrate; many observers have also attested the value of richness in vitamins. The following will meet the daily requirement pretty well for average activity:

Breakfast

Cooked cereal with cream but *very little* sugar
2 soft-cooked eggs
3 slices bacon
1 or more slices toast, or white bread, with much butter
Tea preferably for its astringency but coffee is permissible; again little or no sugar

Luncheon and Dinner

Lean cooked meats, generous portions
Baked potatoes or rice, much butter
White bread and butter
Milk as much as wished
Gelatin dessert, cream but no sugar
Tea or coffee if habituated

Raw fruits had best not be allowed for quite a while but the strained juices may be taken unsweetened and in much moderation; no leafy or vegetable salads. Work sugar and green vegetables back into the diet very slowly. The studies of Faust and associates (1936) in dogs indicated great value for the oral (not parenteral) administration of liver as in pernicious anemia; convincing trials in the human are still lacking. Rogers (1933) stated that alcohol should not be taken by patients with amebiasis as it "strongly predisposes to amebic hepatitis and liver abscess." Hummel (1937) would also interdict tobacco. Ghosh (1939), in chronically recurring cases in India, regulated the diet to maintain an alkaline reaction of the feces instead of the acid reaction favored by *E. histolytica*; means to this end are the following: reduction in meat, rice, macaroni, cereals, bread; increase in fruit and vegetables; addition to the diet of figs, molasses and raisins (but this is hardly the high protein-low carbohydrate diet advocated above).

While in general the chief propagator of the disease is not the acutely ill patient but the convalescent or chronic carrier of the cysts, it is nevertheless

desirable to treat the excreta and bedclothes in the acute stage much as is done in typhoid fever; attendants must also look scrupulously to the cleanliness of their hands.

TREATMENT OF COMPLICATIONS

Abscesses of the lung and of the brain require the usual treatment for these conditions plus the systemic use of emetine. Peritonitis, perforation, or severe bowel hemorrhage requires complete rest or immediate surgery, largely depending on the patient's condition. In liver abscess it is now generally agreed that emetine combined with aspiration is much preferable to surgical drainage when there is no secondary infection; unless the symptoms *demand* immediate aspiration it is often well to give the emetine full chance, for if this is done the puncture can be avoided not infrequently. Berne (1942) treated 63 cases as follows: 19 patients, including 3 who had hepaticobronchial fistula, were treated with emetine alone and all recovered; 18 patients were treated with emetine and subsequently aspirated and all recovered; 26 patients were treated by open surgical drainage, some with and some without emetine, and 14 of them died. Ochsner and DeBakey (1943) reported a mortality of 3.6 per cent in 83 cases in which emetine with or without aspiration was employed and a mortality of 22.1 per cent when open drainage was performed. Walters *et al.* (1944) stated the opinion that open surgical drainage should be employed only when acute perforation into the peritoneum or pleura is actual or impending or when there is proved pyogenic contamination. In a case of hepatic abscess in which emetine and aspiration were unable to effect complete cure because of secondary infection of the cavity with a hemolytic streptococcus, Noth and Hirshfeld (1944) successfully controlled the condition by the injection of penicillin into the cavity; the patient was given a total of 830,000 Oxford units during a period of fifteen and one-half days, injection being made at four-hour intervals beginning with 25,000 units for the first eight doses and then 10,000 units for all doses during the next seven days and 5,000 units for all subsequent doses. In retrospect the authors felt that as good results might have been achieved with somewhat smaller dosage and that perhaps occasional aspirations of material from the cavity might have been beneficial.

The specific amebacidal agents other than emetine, all being at least potentially hepatotoxic, should not be employed in cases of known liver abscess until emetine, with or without aspiration, has brought about subsidence of the liver involvement.

TREATMENT OF THE CARRIER

In the treatment of the carrier we can only employ the remedies described for use in the acute sufferer from amebiasis.

PROPHYLAXIS

Dietary Precautions.—Brief sojourners in the tropics where the incidence of amebiasis is highest should endeavor to eat only thoroughly cooked foods and drink only boiled water or bottled beverages which are known to have been sterilized. But this is difficult of accomplishment and of course does not afford protection against subsequent and extraneous contamination by food handlers and other carriers.

Purification of Drinking Water.—When boiling is not feasible, it is said that purification of water may be accomplished by placing 10 drops of hypochlorite (chlorinated soda solution) in 1 pint (about 2 ordinary tumblerfuls) of water, letting it stand five minutes after stirring, and then adding enough sodium

thiosulfate (photographer's "hypo") to overcome the disagreeable chlorine taste; usually a crystal (or a *very* small pinch if in powdered form) of the "hypo" will suffice. For purification of larger quantities, 1 teaspoonful of hypochlorite should be used per gallon of water. One should add, I think, that Brady *et al.* (1943), after reviewing their own studies and those of others, were none too sanguine about the protection afforded by the chlorination of raw water.

Drug Prophylaxis.—Of all the drugs, diodoquin seems best suited for prophylactic use since it does not give rise to disagreeable symptoms and is highly effective. The same dosage is used prophylactically as therapeutically. Craig (1940) said that it should be employed for twenty days even though the region is left before the expiration of that period; if the visit is longer than twenty days the course may be repeated after an interval of a week.

BACILLARY TYPE

(*Shigellosis*)

Bacillary dysentery is an infectious disease caused by *Shigella dysenteriae*, of which there are apparently four main strains—Shiga-Kruse, Flexner, Hiss and Sonne-Duval—and very many related varieties. The cases range in severity from very mild to fulminating choleraic types; very many cases, too, are likely never recognized for what they are since this disease is a great mimic. In the average "typical" case the onset is sudden with rise in temperature, severe abdominal pain and tenesmus, early appearance of bloody and mucous diarrhea, and the symptoms of toxemia and dehydration. There is diffuse inflammation of the colon and lower part of the ileum, with ultimately necrosis and extensive ulceration and very rarely perforation. Adults between twenty and thirty and infants under two years of age are the most susceptible. The disease is endemic in the tropics and occurs sporadically elsewhere, but it may become epidemic anywhere during periods of crowding, bad sanitation, privation and other causes not yet understood. Flies, ants possibly (Griffitts, 1942), contaminated food and water, and human carriers are the agents of its dissemination. It is now believed by many observers that most tropical dysentery is of the bacillary and not the amebic type; the asylum and prison dysenteries and some of the summer diarrheas in infants also belong in this group; according to Callender (1943), bacillary dysentery is the principal factor in the production of noneffectiveness through diarrheal disease in all active military operations. Mortality varies widely with the locality and the particular outbreak, being from 2 to 80 per cent. Death is caused by toxemia, or later in the disease by peritonitis or inanition; circulatory failure or intercurrent pneumonia is frequently the cause during epidemics. Bacillary dysentery is notorious for the invalidism it causes; Felsen (1942) estimated that distressing chronic sequelae occur in about 8 per cent of cases, and Weil (1943) considered that this figure was not at all too high. Many individuals harbor the dysentery bacilli for months during their convalescent period and, indeed, even individuals with no history of recent infection and no intestinal complaints have been shown to be carriers to a greater extent than was formerly believed; Watt *et al.* (1942) found 2 per cent of carriers among 6324 such individuals in New York City and 3.2 per cent in 1659 persons examined in New Mexico, Georgia and Puerto Rico.

Therapy

Sulfonamides.—All of the sulfonamides, with the exception of sulfanilamide, are effectively used in the treatment of bacillary dysentery, marked fall in temperature and leukocyte count and decided clinical improvement often occurring within twenty-four to forty-eight hours; there is also early reduction in the number of stools and great improvement in their character as to blood, pus, or mucus content. Eisenoff and Goldstein (1943) used sulfathiazole and sulfadiazine in doses of 1 grain (60 mg.) and sulfaguanidine and succinylsulfathiazole (sulfasuxidine) in doses of 2 grains (120 mg.) per pound of body weight for an average of four days in an outbreak of Sonne dysentery involving 50 children. The stools of 90 per cent of the children were cleared with the one course and the remaining 10 per cent cleared with one or two additional courses of treatment; this was remarkable testimony to the efficacy of this group of drugs since Sonne infections usually yield less readily than do those due to the Shiga-Kruse, Flexner or Hiss strains. Eisenoff and Goldstein felt that no advantage could be claimed for one drug over any of the others, and indeed there is a good deal of testimony in the literature to that effect. The dosage of sulfadiazine and sulfathiazole recommended in the War Department Technical Bulletin (War Medicine, 7, 36, 1945) was an initial dose of 2 Gm. followed by 1 Gm. four times daily, the use of the drug to be continued for a minimum of five days and not to be discontinued until two days after clinical recovery; the dosage of sulfasuxidine and sulfaguanidine was stated to be 5 Gm. four times daily and it was considered permissible alternatively to administer 3.5 Gm. of sulfaguanidine every four hours day and night. The tendency in recent years has been to employ sulfaguanidine or sulfasuxidine in preference to the other members of the series because they are absorbed much more slowly from the intestinal tract and therefore can exert their local bacteriostatic effect with a minimal likelihood of inducing systemic reactions. Sulfasuxidine has come to be preferred to sulfaguanidine because the latter is sometimes absorbed rather erratically and as its conjugated form is relatively insoluble in the urine it has at times given rise to urinary tract disturbances. Blood concentrations of sulfaguanidine as high as 10 to 16 mg. per cent are sometimes recorded, but I have seen no record of a sulfasuxidine content above 2 mg. per cent—for example, in the study of Smyth *et al.* (1943), in the 12 sulfaguanidine-treated cases there were 2 instances of concentrations a little above and a little below 8 mg. per cent, 1 instance of 10 mg. per cent, 1 of 14.3 mg. per cent and 1 of 16.6 mg. per cent, whereas in the 24 sulfasuxidine-treated cases in no instance did the concentration exceed 1.45 mg. per cent. Roberts and Daniels (1943) made a point of the advisability of employing adequate dosage of opiates to check the diarrhea in the beginning so that these drugs will not pass too rapidly through the bowel. Indeed, the loss of efficacy of sulfasuxidine in the presence of a watery diarrhea is the chief drawback to the drug. Poth and Ross (1944) are studying phthalylsulfathiazole (sulfathalidine) which they find does not tend to liquefy the stools; this new drug has been found to be highly effective in bacillary dysentery in a dosage of 0.04 Gm. per kilogram body weight every four hours for 12 doses, and then half this dosage at four-hour intervals until diarrhea ceases or for no more than a total of seven days if improvement does not take place (these doses would correspond for the man of 70 kilograms or 150 pounds to 2.8 and 1.4 Gm. respectively).

Najjar and Holt (1943) found that in a symptom-free subject given 1.5 Gm. of sulfasuxidine every four hours for one week, the vitamin B_1 (thiamine) content

of the feces was reduced to zero, normal thiamine value reappearing a few days after the drug was discontinued; these observers felt that their studies demonstrated the inhibition of the biosynthesis of thiamine since they felt that they had ruled out the possibility of the direct destruction of thiamine by the drug or to some interfering effect of the drug on thiamine determination. The important clinical point, it seems to me, is that the administration of large doses of thiamine might be advisable during the time that sulfasuxidine or sulfaguanidine is being employed.

Cathartics.—Prior to the advent of chemotherapy in this disease the attempt was made to lessen absorption and promote elimination of toxins by thoroughly washing out the bowel with cathartics and keeping it washed out, but this treatment is now surely outmoded since it is highly desirable that the sulfonamide remain in the tract.

Adsorbents.—Kaolin and charcoal were used before the introduction of the sulfonamides in the hope of adsorbing some of the toxins, in which capacity it would seem that they were oftentimes quite effective: kaolin up to 300 Gm. in a pint of hot tea to be drunk during the day; charcoal, preferably of animal origin because of its smaller particles, up to 80 Gm. But the administration was always difficult and it is doubtful if they will any longer have a place in this therapy.

Saline and Dextrose.—It is of course of great importance to combat the dehydration and acidosis and salt deprivation which occur with astonishing rapidity in fulminating cases, even though the sulfonamides are being administered. Parenteral administration of dextrose in Locke's solution is the best way to combat these conditions, but if acidosis is severe it may be advisable to use lactate-Ringer's solution, which has the advantage over a solution containing sodium bicarbonate that it can be sterilized by boiling: sodium chloride 6.0 Gm., sodium lactate 2.7 Gm., potassium chloride 0.4 Gm. and calcium chloride 0.2 Gm.

Shock.—See the article on Shock for the handling of this situation.

Relieving Pain.—Though morphine or dilaudid may have to be administered in the beginning of severe cases, colicky pain and tenesmus of average severity will be relieved by a few doses of some such prescription as the following:

℞	Codeine phosphate	ʒss	2.0
	Chloral hydrate	ʒv	20.0
	Tincture belladonna	ʒv	20.0
	Compound tincture cardamom to make	℥iv	120.0
	Label: 1 teaspoonful every four hours.		

Hot rectal irrigations are also used to combat tenesmus, and the administration by mouth of 1 drachm (4 Gm.) of bismuth subcarbonate at four-hour intervals is said to be helpful. Heat applied to the abdominal wall is recommended.

Polyvalent Serum.—Even before the advent of the sulfonamides it was the consensus that in mild cases likely to recover quickly the cost of the serum plus the probability of serum sickness contraindicated its use, while in severe cases it was by no means agreed by all authorities that serum treatment of the cases effectually lowered mortality; where used, however, it was advised that it be given early, intravenously and in an average dose of 200 cc. for the adult. It is extremely unlikely that serum treatment will hold any place at all in competition with chemotherapy.

Convalescent Serum.—Felsen (1940) advocated the intramuscular injection of 100 to 200 cc. of pooled convalescent serum (adult dosage) within the first twenty-four hours, or the transfusion, if compatible, of double these quantities of whole blood from a recovered donor. He collects blood from convalescent acute cases at about the end of the third week.

Bacteriophage.—According to statements of German medical officers during War II, bacteriophage was the standard treatment for bacillary dysentery in the forward areas of the German army in Africa. Large quantities of this bacteriophage were captured during the Axis retreat from El Alamein, and Boyd and Portnoy, in 1944, made a valuable controlled study of its efficacy on German prisoners. It was concluded from this study that bacteriophage fails to exercise *in vivo* the potent properties which it exhibits *in vitro*.

Vaccines.—The use of vaccines in the treatment of acute dysentery has come to nothing. It has been suggested, however, by Silverman and Friedrichs (1943) that arthritis, myocarditis, vascular dysfunction and even obstructing spasm of the colon as seen in chronic dysentery are probably manifestations of protein hypersensitiveness to the bacilli infecting the patient and that the attempt to desensitize such patients with autogenous vaccines would be in order.

Diet.—It is difficult to make any distinction between dietary treatment here and in acute severe cases of amebic dysentery except in the one item of milk, which apparently no matter how given, whether fresh, diluted, or disguised, aggravates the colic; beef or chicken broth must be substituted. Strangely, Corner (1935), with considerable experience in severe outbreaks, stated that occasional ice cream is well borne. The excessive amount of butter in the amebic dysentery diet should be eliminated in severe cases of the bacillary form since fat is likely to increase this diarrhea. Block and Tarnowski (1941) felt that bananas are a distinctly valuable supplement to the diet, and Winters *et al.* (1939) had good success with pectin-agar (see succeeding article on Infantile Diarrhea). There are also in existence some preliminary experimental data indicating that possibly a hitherto unsuspected type of vitamin deficiency underlies dysentery susceptibility, but there is nothing as yet definitely applicable to man.

Nursing Care.—The patient must be kept as quiet as possible since the very frequent stools are terribly wearing even in the absence of toxemia. To keep him warm will sometimes tax the ingenuity of nurse and physician. Isolation and scrupulous attention to the personal hygiene of patient and attendants are fully as important here as in typhoid fever.

Chronic Cases.—In these days of sulfonamide therapy the procedures to be described below very rarely need be resorted to. Appendicostomy and washing out from above used to be much advocated, but since it has been amply shown that the entire colon can be filled from below, I do not believe it is any longer a rational treatment. Smyly said that cecostomy, with the opening of an artificial anus to give the colon complete rest for three months, might prove a satisfactory treatment in exceptional cases. Most patients respond to less heroic measures in a shorter time. The silver salts are used locally: an enema of 500 cc. of a 1:100 argyrol (mild silver protein) solution, or 1:500 protargol (strong silver protein). Copper sulfate is used in 0.5 per cent strength, or 2 per cent tannic acid solution; the De Rivas technic of irrigating with copper sulfate solution, as in amebic infection, has been favorably reported upon. These solutions, the silver salts especially, stimulate an acute reaction and a

reparative process, but the balance between inflammation and repair is not always easy to strike; they should therefore not be repeated too often. Ten per cent silver nitrate, rarely stronger, may be applied directly to the rectal ulcers.

The Carrier.—There have been a number of reports of the successful sterilization of carriers of Shigella by the use of sulfaguanidine or sulfasuxidine in full treatment dosage for one week. The study of Hoagland *et al.* (1943) is typical: they treated 30 carriers with sulfaguanidine and 15 with sulfasuxidine daily for six days; dysentery bacilli disappeared from the feces of every patient, the criterion of cure being a minimum of 9 consecutive negative reports of feces cultures made after (*i.e.* from the fourth day following) cessation of treatment.

Prophylaxis

Scott (1943) treated 50 individuals exposed to Sonne dysentery in an institutional outbreak with 0.5 Gm. of sulfaguanidine three times daily for about seven days, the drug being started on the fifteenth day of the outbreak after 20 cases had already occurred. No further cases developed, but as this study was uncontrolled it is not possible accurately to evaluate it. Lucchesi and Gildersleeve (1943) gave 0.3 Gm. of sulfaguanidine per kilogram per day for the first day and one-half this amount for the following two days to 45 children exposed to Flexner dysentery, 48 children in an adjoining wing of the institution remaining untreated as controls; no new cases developed among the treated children but 4 developed among those that were not treated. In the study of Yannet *et al.* (1944) after the outbreak of Sonne dysentery in an institution housing girls of an average age of seventeen years, 22 girls were placed on sulfaguanidine at 2 Gm. daily for fourteen days and 31 were left untreated as controls, all the girls eating in a common dining room and using common play rooms and bathrooms; 6 girls in the control group developed typical dysentery and none in the treated group. No such definitive studies employing sulfasuxidine have come to my attention as yet but the drug must surely be just as effective as sulfaguanidine in prophylaxis.

INFANTILE DIARRHEA AND VOMITING

In the good old days when privies were neatly whitewashed and there were still plenty of corner pumps and horses and flies, and when the milkman drove about ringing his big bell in the heat of the day and ladling his wares from open cans into nicely sun-warmed pitchers and jugs—in those far-off times a goodly proportion of infants quickly sickened and died in the late summer months of a condition known as "cholera infantum." Nowadays the scene is changed and "summer diarrhea" as such has greatly diminished in the areas of modern civilization, but nonetheless infantile diarrhea and vomiting is still seen distressingly often throughout the year, particularly in artificially-fed infants and especially among the poor and less well-nourished classes. The etiology of these cases is complex: some seem due to dietary errors, doubtless many are really cases of bacillary dysentery, in some instances there is infection with a member of the *Salmonella* group or with a streptococcus or some other organism, in some instances the symptoms are definitely secondary to infection elsewhere. Mortality is still high unless expert therapy is begun very early.

Therapy

Sulfonamides.—Taylor (1941) reported the successful employment of sulfathiazole in alternate cases in a series of 27 patients. The stools returned to normal in 3.2 days in the treated group, in 15.6 days in the untreated; there were no deaths in the treated group, 2 in the untreated. Tudor (1942) compared sulfathiazole and sulfaguanidine in alternate cases in his series and found that although both sulfonamides were satisfactory sulfathiazole seemed to be more effective in the parenteral diarrheas; Glaser and Bruce (1944) said that they have tried to treat the nonspecific type of diarrhea with sulfathiazole and the specific diarrhea with sulfaguanidine but that due to delayed diagnosis the specific cases are sometimes treated with sulfathiazole. Indeed there would seem to be no advantage in using the nonabsorbable sulfonamides in these cases because the newer agents, sulfadiazine and sulfapyrazine, have been shown to be very effective by both Tudor (1943) and Menchaca (1944) in series large enough to be of significance. The dosage in which all the drugs of this series is employed is usually 0.1 Gm. per kilogram of body weight ($1\frac{1}{2}$ grains per 2.2 pounds) per twenty-four hours, the patient usually being given one half of the initial twenty-four-hour dose immediately and the rest in equal portions every four hours.

Fluids and Alkalis.—The reader should mark well that the fine record made by the sulfonamides in the treatment of infantile diarrhea and vomiting is predicated upon the understanding that despite the use of these agents dehydration has to be vigorously combated in the beginning in all severe cases. The usual routine is to give intravenously 5 per cent dextrose solution, or physiologic saline solution, or 5 per cent dextrose in the saline; they should be given at the rate of 15 to 30 drops per minute for the first 200 or 300 cc. but thereafter the rate must be cut down rather sharply; Alexander and Eiser (1943) said that infants under three months require a slow flow of 8 to 10 drops per minute while older children will tolerate 12 to 15 drops per minute, but certainly the rate of flow and the total quantity of fluid given need to be adjusted for the baby's weight, the degree of dehydration, the amount of pyrexia and the amount of fluid which the infant is taking by mouth. One must watch these patients very carefully, too, and at the earliest sign of edema, such as puffiness of the hands and feet, eyes, scrotum or vulva, the fluid must be immediately discontinued since an infant can be easily "drowned" with parenteral fluid. Acidosis must oftentimes be combated also, but Mitchell (1939) well pointed out that the routine administration of sodium bicarbonate to all infants with diarrhea is unjustified since actual alkalosis may thus be caused and the diarrhea may be increased if the alkali is given by mouth, and since the administration of fluids as above may alone suffice. Indeed, he advocated alkali administration only if determinations of the carbon dioxide content of the blood indicate its necessity—but such determinations are certainly not possible in all types of practice. In general, coma or impending coma, hyperpnea or convulsions (but the latter may also indicate that too much alkali has been given!) are good indications that the child is suffering from acidosis. Sodium bicarbonate should then be given until the urine turns alkaline. Mitchell said that this will be accomplished with 30 to 45 grains (2 to 3 Gm.) in infants and 60 to 75 grains (4 to 5 Gm.) in older children, but in acidosis many times these quantities may have to be given. The sodium bicarbonate may be administered in 5 per cent solution intravenously, or $\frac{1}{6}$ molar sodium lactate solution (which is higher in sodium lactate content than Hartmann's

solution) may be used instead; the lactate solution has the advantage over sodium bicarbonate solution that it can be sterilized by boiling. Minot *et al.* (1934) suggested the addition of a calcium compound to ward off convulsions but I do not find evidence in the literature that this suggestion has been followed.

Diet.—It is almost the rule to starve the patient for twenty-four hours (some pediatricians permit very weak tea with saccharin) and then to begin feeding again with skimmed protein or lactic acid milk in gradually increasing amounts. Glaser and Bruce (1944), however, stated that since abandoning this method they have had better results than in earlier years; beginning twelve hours after admission to the ward they offered full bottles to their infants and gave them as much as they would take, the orders reading "buttermilk as tolerated" or "skimmed boiled milk ad libitum." These observers found that the children regulate their intake according to their appetite, and they find it a great advantage to be able to tell the mother to allow the infant to take as much as he wants. Upon cessation of the diarrhea, *i.e.*, when the stools have been normal from two to four days, they return the infant to the normal formula during a period of twenty-four to forty-eight hours by replacing fractions of buttermilk by formula.

Bismuth and Opiates.—During the height of the diarrhea many men employ a bismuth and paregoric mixture such as the following:

℞	Camphorated tincture opium	ʒj	4.0
	Bismuth subcarbonate	ʒj	4.0
	Mucilage acacia	℥j	30.0
	Anise water to make	℥iv	120.0

Label: For infant up to two years, 1 teaspoonful every three hours.

However, most pediatricians decry this practice and resort to the use of these drugs only in extreme cases.

Treatment of Shock.—In some instances a severely dehydrated baby may be collapsed when first seen and will require to be treated as described in the article on Shock. Alexander and Eiser (1944) found that in administering serum or plasma to infants it is simpler to use one-half strength solution to obviate the technical difficulty of getting the rather sticky full-strength fluid to run through a slow drip; they also warned against too enthusiastic serum or plasma therapy in small infants, reporting 4 consecutive cases in which the continuous infusion of half-strength serum caused so much tissue fluid to be drawn into the blood stream as to initiate serious circulatory embarrassment.

Apple (or Banana) Diet.—In Germany some years ago there developed out of an old folk remedy the so-called "Moro-Heisler apple diet" for the treatment of all sorts of diarrheal conditions in infants and young children. Enthusiasm ran very high for this sort of treatment for a while but I have not seen any very recent references to its employment. Ripe, mealy eating apples, cored and grated to a fine pulp (with or without previous paring) were given in quantities of 1 to 4 tablespoonfuls each hour during the day. If the acid flavor was objected to an inch of ripe mashed banana was added to each spoonful of apple. No other food was given. Patients took from 10 to 50 spoonfuls per day and it would seem that the more the better. Termination of the diet was made twelve hours after the appearance of formed or semiformed stools, usually in twenty-four, but perhaps thirty-six or more, hours after beginning it. Mitchell (1935) used the following transitional diets for a few days in bringing the patient back to full feeding:

	Infants.	*Children.*
Breakfast:	Cooked cereal (no milk) Apple pulp (4 tablespoonfuls)	Cereal (with skimmed milk sufficient to make edible) Toast Cocoa (made with water)
Midmorning:	Apple pulp (1–4 tablespoonfuls)	Apple pulp Cracker (saltine or soda cracker)
Lunch:	Clear broth or bouillon Rice Junket (made from skimmed milk)	Broth or bouillon Rice Scraped beef or chicken Toast or cracker Junket (from skimmed milk)
Midafternoon:	Gelatin	Gelatin and cracker
Supper:	Cooked cereal Apple pulp	Cooked cereal Toast Cocoa Apple pulp or banana

Skimmed milk, whole milk junket, baked potato, custard, jam, marmalade and cream cheese may be added next. Cream is gradually returned to the milk, and meat, vegetables and fruits allowed in increasing amounts. Reappearance of diarrhea necessitates a brief return to the apple diet.

In the later reports apple powder had largely replaced fresh raw apple for use in treating the diarrhea. It is given in 4 to 10 per cent solution in water, weak tea or skimmed milk, 24 to 36 Gm. for infants under one year, 80 to 100 Gm. for older children. Many men also replaced apple with banana with good success, and latterly banana powder more or less replaced the fresh fruit.

Pectin-agar.—Malyoth having shown that pectin and cellulose are the two ingredients of apple likely responsible for its therapeutic effect, Winters and Tompkins (1936) introduced a pectin-agar preparation for the treatment of these diarrheas. This seemed adequately to replace apple or banana, fresh or powdered, and to be very simple to use. The ingredients of this preparation as described by Howard and Tompkins (1940), are pectin 6.3 per cent, agar 4.3 per cent, dextrimaltose 89.4 per cent. One cup (8 ounces) of this powder yields 480 calories and serves well as a basic formula for the diets of nurslings and young children. For nurslings, 8 ounces is cooked ten minutes in a double boiler with 24 ounces of milk, poured into nursing bottles while still hot; when rewarmed and shaken it will feed easily through a nipple with enlarged openings. Since each ounce of this mixture contains 40 instead of the usual 20 calories it should be fed in only half the usual quantities, fluid being administered otherwise. For children six months to two years, 8 ounces of the powder is cooked with only 16 ounces of milk, or it may be cooked in a smaller amount of water and fruit juices added up to full volume; flavoring agents such as vanilla or chocolate may be added, and the mixture may be frozen if preferred.

EPIDEMIC DIARRHEA OF THE NEWBORN

In recent years a number of epidemics of severe intestinal intoxication occurring as localized outbreaks among a hospital's population of newborn infants have been reported from several cities in the United States, Canada and England. Both sexes and all races are attacked but only during the first two or three weeks of life, older children and adults being apparently immune The chief symptoms are the passage of numerous watery yellow stools without

blood, mucus, or pus, great distention, occasional vomiting, marked dehydration, great and precipitous weight loss, possibly but not invariably fever, drowsiness, shock and a very high mortality. The disease is extremely contagious but the etiologic agent has not yet been determined, though the study of Buddingh and Dodd (1944) pointed strongly toward a virus in the causative role. In an outbreak in one of the Milwaukee hospitals in 1938 breast-fed infants either did not contract the disease or if they did so were able to survive the attack; this has also been the experience elsewhere. In our epidemic acute enteritis was found in 87 per cent of the 16 babies autopsied, with pneumonia the next most frequent finding, though the latter predominated over all other findings in only 3 instances; in several instances there was aspiration pneumonia and in 2 of these it seemed to be the cause of death as there was no evidence of an enteritis in these cases. However, in other epidemics elsewhere enteritis has not been always a predominating finding; Sakula (1943) reported findings suggesting an acute toxic condition rather than an intestinal infection, the liver, thymus and suprarenals being notably affected.

Therapy

These epidemics do not respond typically to the measures employed in bacillary dysentery and ordinary infantile diarrhea. In the Milwaukee outbreak (Cron, Shutter and Lahmann, 1940) the sulfonamides were tried and failed, but since the newer drugs of this series were not available at that time one may still hope for something from this type of chemotherapy; indeed, Twyman and Horton (1943) felt that sulfasuxidine had been successfully employed in the epidemic reported by them. Transfusions from donors given a sulfonamide twenty-four hours previously, convalescent serum, autogenous vaccines, all failed in our epidemic. It was thought that breast milk, begun as soon as possible after a supply was obtained, was helpful, but the only babies who either escaped or survived the epidemic were those nursed upon human milk from the time of their birth. Lyon and Folson (1941), in an epidemic in Huntington, West Virginia, felt that citrated whole blood (30 cc. injected into the gluteal region) from a patient recently convalescent from clinical influenza was astonishingly helpful in 3 of their cases, and they suggested the possibility that epidemic diarrhea of this type may be an expression of infection with influenza virus in the newborn. Anderson and Nelson (1944) felt that the most marked improvement in the infants involved in their epidemic resulted from the raising of a low carbon dioxide combining power of the blood to the normal range by the parenteral administration of alkalis.

It seems to be the consensus that to safeguard against outbreaks of this dreadful malady some means must be found for increasing the already prodigious efforts to attain asepsis in the maternity and newborn quarters in modern hospitals. The Milwaukee group is making a strenuous effort to increase the incidence of breast feeding as a precautionary measure of apparently proved value.

FLAGELLATE DYSENTERY

(*Giardiasis, Lambliasis, Balantidiasis*)

In recent years it has become generally recognized that infestation of the intestinal tract, particularly of the duodenum and upper part of the ileum, with the flagellate protozoan *Giardia* (*Lamblia*) *intestinalis* is quite common throughout the world, and there is some evidence that these flagellates occa-

sionally invade the gallbladder and possibly even the higher biliary passages and give rise to a quite variegated array of symptoms. It would seem that, since a remittent type of diarrhea characterized by the frequent passage of liquid or semisolid stools of clay-brown color and foul odor but only very rarely containing a little mucus or a tinge of blood, is the disturbance most frequently associated with this infestation, it would probably be wise to consider giardiasis differentially in any case of abdominal discomfort with flatulence, diarrhea, steatorrhea and dysentery. I say *it would seem* advisedly because there are still individuals of considerable experience who doubt the pathogenicity of *G. intestinalis;* however, the improvement in patients who are rid of their infestation by the employment of atabrine (see below) strongly supports the contention that the presence of Giardia is not merely coincidental in these cases. Possibly Treu's (1944) proposed separation of the cases into three groups is a justifiable one which will serve to reconcile the disparities in the experience of observers all over the world: he feels that the mere presence of *G. intestinalis* in the stool of normal subjects, which is a frequent occurrence especially in children, is of no clinical interest; that heavy infestations of the colon when the organism suddenly multiplies enormously for some unknown reason may produce a bout resembling dysentery but is self-limiting in duration; and that there is a type of infestation in the small intestine which is very chronic but characterized by a periodicity of symptomatic episodes. Welch's (1943) study indicated that the eosinophilia may be characteristic of severe giardial infestation. In Drenckhahn's (1943) case there was jaundice associated with the presence of large numbers of the flagellate in the bile content. Similar but perhaps not entirely identical forms of this organism infest many domestic animals.

Balantidium coli, a ciliated protozoan that is a common organism in the pig, is capable of establishing itself in the colon of man and giving rise to symptoms much resembling those of amebic dysentery. There is extensive ulceration, invasion of the submucosal tissues and loss of considerable blood, together with the passage of much shed necrotic epithelium in the diarrheal stools. Balantidiasis has been reported from many parts of the world but usually only a small group of cases in closely associated individuals, or an isolated instance of the infection, is described. DeLanney and Beahm (1943), reporting a case of their own, brought the number of cases recorded in the United States to only 49 so far as I know. Mackenzie and Bean (1938) believed that theirs was the first case reported in England.

Therapy

Until recently in giardiasis the whole gamut of amebicidal and anthelmintic drugs has been run without much success, but now it seems that a truly specific agent has been found in the synthetic antimalarial drug atabrine (quinacrine, mepacrine). Galli-Valerio (1937) first reported its successful use in Switzerland and quickly thereafter confirmation came from practitioners in several other countries. Hartman (1943) said that at the Mayo Clinic approximately 75 patients had been treated with but one failure from one course of treatment, a course consisting in the administration by mouth of a tablet of $1\frac{1}{2}$ grains (0.1 Gm.) three times daily for five days. Ormiston *et al.* (1942) gave only $\frac{1}{6}$ of a tablet three times daily to children under two years of age. In an official bulletin issued by the Medical Research Council in England in 1943, the following dosage was

recommended: up to five years, 0.1 Gm. daily; five to twelve years, 0.2 Gm. daily; twelve years and over, 0.3 Gm. daily; infants one year and under not to be treated. Treu (1944), in India, said that he had repeatedly made the puzzling observation that atabrine cures the symptoms of giardiasis rapidly but does not always eradicate the infestation. It is now customary in the practice of many men to give two and sometimes three courses of treatment with an interval of a week or ten days between. Katsampes *et al.* (1944) stated that after the elimination of the organism through the use of atabrine the absorption of vitamin A, which they found seriously interfered with in giardial infestations in children, was much improved; in control patients with celiac disease treatment with atabrine did not affect the absorption of vitamin A.

At the present writing the successful use of atabrine in balantidiasis has not been reported. All the amebacidal drugs and the anthelmintics have failed to give consistent results precisely as in giardiasis, but in individual instances there are successes reported with several of them; for example, DeLanney and Beahm (1943) used diodoquin satisfactorily in a single case, 10 tablets of 0.25 Gm. each being given daily for twenty days. Perhaps the cases of Young and Burrows (1943) are more noteworthy since there were 7 infections in the series: in 2 cases, two doses per day of 0.25 Gm. for ten days eradicated the infection and in 2 others a second course did so; in 1 case receiving the drug in smaller amounts the infection disappeared; in the other 2 cases a course of 1.0 Gm. per day (two doses of 0.5 Gm. each) for ten days accomplished eradication. Mackenzie and Bean made a wide departure in therapy by employing Loeffler's methylene blue because of its ability to stain the organism. They had only one patient to treat, but in her 2 retention enemas of the stain, given twenty-four hours apart followed by a third two weeks later, seemed to clear the stools permanently of both ciliated and cystic forms of the organism. Actually, however, these workers had been preceded by Chase and Tasker, who, in 1917, had used this stain both in enemas and by mouth; they used only the medicinally pure drug (methylthionin chloride), not that employed in staining, because the latter contains traces of zinc, and gave 2 grains (0.12 Gm.) every three hours by mouth and enemas of the 1:500 up to 1:200 aqueous solution (retained fifteen minutes) once or twice daily.

STRONGYLOIDES DYSENTERY

(See the section on *Worms*)

EPHEMERAL FEVER

(*Febricula*)

Certain fevers of one or at most three days' duration, unaccompanied by any demonstrable causative lesion and disappearing as rapidly as they appear, have long been denoted "ephemeral" fevers for want of a better name. Sometimes there is nausea, vomiting, colic and perhaps chills. It has been thought that exposure to sewage gas and foul odors from other sources is responsible for this type of fever, but it is extremely likely that as our diagnostic means and skill improve it will eventually be recognized that all these cases are abortive attacks of one of the clearly recognized infectious diseases.

The fevers of unknown origin frequently seen in youngsters following a sudden change of environment probably belong in this category.

THERAPY

Nothing, of course, has been evolved beyond the usual palliative measures designed to ease such slight symptoms as are met with here.

EPIDEMIC ENCEPHALITIS

(Encephalitis Lethargica, St. Louis Encephalitis, Japanese Type B Encephalitis, Australian X Disease, Equine Encephalomyelitis, Toxoplasmic Encephalitis, Russian Encephalitis, Sporadic Encephalitis of Unknown Origin)

Encephalitis lethargica first appeared as an apparently new disease on the Continent in 1915 and for a few years thereafter was epidemic throughout the western world. Many investigators believe this outbreak to have been identical with the "nona" of the 1890's and indeed many earlier visitations, the earliest of which perhaps was that described by Sydenham as having prevailed in London in 1673 to 1675. Since 1926 only an occasional sporadic case has been seen. It was thought that this encephalitis of von Economo was caused by a filtrable virus, perhaps related to but not identical with those of herpes and influenza, but this fact was never established. The acute clinical manifestations were very complex and appeared either suddenly (often after a period of enforced activity) or gradually; often, but by no means invariably, there were the following symptoms: increasing drowsiness, slight fever, diplopia or other eye muscle disturbances, salivation and head cold. After the patient took to bed he usually lay relaxed and absolutely quiet, with one or both lids ptosed, apparently but not actually asleep; indeed, insomnia was of frequent occurrence despite the mask of deep stupor. Other patients manifested evidences of motor irritation from the beginning—movements of the pill-rolling, Parkinson type—or they were choreoid, or clonic-spasmodic. Mentality was usually impaired, especially as to memory, attention and orientation. Emotional disturbances were common, and in some cases marked alterations of character and oddities of behavior were outstanding features. Delirium sometimes alternated with periods of stupor. In many cases there was an increase in globulin and sugar and a slight increase in the cell count in the spinal fluid. The disease occurred in the winter and spring and affected principally individuals in the third and fourth decades; the mortality was between 25 and 40 per cent. Convalescence was very slow, and the sequelae, from which recovery was also very slow if it occurred at all, were much dreaded; persistent insomnia or prolonged somnolence; Parkinson-like syndromes; autonomic pupillary, respiratory, cardiac, sphincter, etc., disturbances; mental impairment; psychoneurotic manifestations, and so on.

The newer types of encephalitis differ markedly from the above. St. Louis encephalitis appeared in several counties in Missouri in 1933 and recurred in that area in 1937. In the first epidemic there were 1097 cases with a mortality of about 20 per cent; the second time the mortality was 24.8 per cent with only 431 cases, most of the deaths in both epidemics occurring in elderly

people. A few other outbreaks of somewhat smaller proportions have occurred in other areas of the United States. St. Louis encephalitis occurs only in the late summer and early fall and affects individuals of all ages but principally in the upper age groups. The attack usually begins with chilliness and malaise, vomiting and often severe abdominal pain, sometimes quite high fever and often a disproportionately slow pulse, grippe-like aches and pains, and early signs of cerebral involvement, such as severe headache and stiff neck, mental confusion and perhaps even delirium, convulsions or coma, tremors and a variegated lot of other neurological signs; but notably absent or at most only transiently present are the ocular manifestations characteristic of encephalitis lethargica. Globulin, pressure and the cell count (predominantly lymphocytes) are usually moderately increased in the spinal fluid but the sugar remains normal in most instances. The course may be very stormy but recovery is usually complete in two or three weeks and mild subjective nervous complaints are the most common residuals (as revealed in the Bredeck *et al.* [1938] follow-up study of the first epidemic in St. Louis). It is believed that many subclinical cases occur during an epidemic.

A number of quite similar outbreaks have been reported from Japan but the mortality there seems to run as high as 50 to 60 per cent. A filtrable virus has been recovered in both St. Louis and Japanese B encephalitis, has been cultured and established in several experimental animals, but it appears that the two viruses are distinct or at least distinctive strains of the same virus. Apparently St. Louis encephalitis occurs only in the United States and Japanese B encephalitis only in Japan. In far eastern Russia a disease similar to Japanese B encephalitis attacks principally adult males who work in the deep forests, but Casals and Webster (1944), of the Rockefeller Institute, compared this virus with several others of the encephalitis group and found it unrelated to all except that of louping ill, a disease of sheep, which it is said to resemble closely; it seems probable that this or a very closely related virus was also involved in the epidemic in Australia in 1917 and 1925 of the encephalitis known as Australian X disease.

Equine encephalomyelitis is a very recently recognized disease in man though it has been known in horses for a long time. The first outbreak in the human was reported in 1938, first from the New England and then from the Western States; I believe that the largest epidemic to date was that in and around North Dakota in 1941, in which there were 1080 cases with 96 deaths. The disease occurs in summer and is clinically very similar to St. Louis encephalitis except that it attacks children mostly, is usually abrupt in its onset and sharp and short in its course, and such permanent residuals as paralyses and mental changes are common. Equine encephalomyelitis has been shown to be due to a filtrable virus recoverable from both horses and man but the eastern and western strains are different; there is also a distinctive Venezuelan strain which is known also to have made its way over to the island of Trinidad, but most of the human infections with this strain have been acquired in the laboratory. It has been reported (J.A.M.A., March 11, 1944) that the encephalomyelitis of Brazil is not caused by the Venezuelan strain but by the eastern strain of our North American type of the disease. The work of several investigators strongly indicates that St. Louis encephalitis, Japanese B encephalitis, and the western and eastern types of equine encephalomyelitis are primarily diseases of birds, the common barnyard fowl as well as wild birds, which have become well adapted to the virus and are very little disturbed by

the infection. It would appear that the infection of man, or the horse and other mammals, by infected mosquitoes is merely an accidental and not a natural part of the cycle, but the mammals manifest severe symptoms because they are not yet well adapted to these viruses. So far, I believe, nine species of mosquito have been convicted as vectors of animal infection but as yet no human case has been proved to have been caused by the bite of one of these insects; nevertheless, Hammon *et al.* grouped these infections together under the term "arthropod-borne virus encephalitides." Russian spring-summer encephalitis is conveyed by the woodtick, and Blattner and Heys (1944), and Smith, Blattner and Heys (1944), showed that St. Louis encephalitis can be conveyed experimentally by the common dog tick and the common chick mite; it was felt that these insects, feeding on birds and mammals, may play an important role in establishing and maintaining a reservoir of infection in these animals but that the disease is probably conveyed to human beings only through the bite of the infected mosquito.

A toxoplasmic encephalitis has been described and is discussed elsewhere in the book (see Toxoplasmosis). And finally, to complete the list of types of epidemic infectious encephalitis, it should be mentioned that sporadic cases of encephalitis are being reported which do not, immunologically at least, fit into the description of any of the above-listed entities.

THERAPY

The description of therapy in this group of diseases will require little space, since there are no specific remedial agents and only symptomatic treatment is available. During the acute stage, light but ample feeding, the forcing of fluids, the keeping of the body clean and the protection of the patient from all annoying sensory stimuli, and in some instances the use of salicylates to relieve pain, are indicated. In the treatment of the insomnia or the excited states, of course, resort must be had to full doses of sedatives (see Insomnia), but it is possibly advisable in choosing among the barbiturates to omit phenobarbital, for the Ziskinds (1937) found that this drug aggravates rigidity in established parkinsonism. During the first St. Louis epidemic (Eschenbrenner, 1934) patients admitted to the Isolation Hospital were given spinal puncture on admission and it was repeated when there recurred evidences of increased pressure or meningeal irritation (Slesinger, 1936, found the routine initial puncture of no advantage). Ten per cent dextrose solution was routinely given intravenously, daily during the severe stage, 750 cc. to adults and correspondingly smaller doses to children. Those with severe signs of cerebral edema were given 50 cc. of 50 per cent dextrose solution intravenously every twelve to twenty-four hours, efficaciously in most cases; Gareau (1941) used this treatment frequently also in his cases of the equine type. Drastic saline purges were used in some instances in the effort to reduce the edema further. Retention of urine in the women and older men sometimes required several catheterizations or the use of the retention catheter for several days. Hyperpyrexia, frequent in the acute cases, yielded to tepid baths, alcohol rubs and the ice-bag to the head. Delirium tremens responded to large doses of paraldehyde.

The sulfonamides have been tried in numerous instances and have always failed; however, Meiklejohn and Hammon (1942) thought that judgment should still be reserved since in an outbreak of St. Louis encephalitis in which they used sulfadiazine they did not have the mortality which they felt might have been expected. Most men see no reason to expect anything from con-

valescent serum, but Slesinger felt that it was of some value in the 22 cases of the St. Louis type in which he tried it.

In the more stuporous patients nasal tube feeding must be resorted to. Barborka's formula (P, 70; C, 195; F, 160; Cal., 2500; fluid, 1760 cc.) follows.

Mix together and boil:
1000 cc. milk — 300 cc. cream
3 eggs — 3 egg whites
120 gm. sugar or lactose
Cool and add the following:
100 cc. orange juice — 15 cc. cod liver oil
3 teaspoonfuls brewers' yeast
Strain through a very fine sieve. Serve at body temperature, 150 to 200 cc. every two hours.

The treatment of the psychoneurotic sequelae, which characterize most notably encephalitis of the lethargic type, being largely systematic attempts at rehabilitation, cannot be described here. Arsenic, iodides, and indeed practically all the other specifics and near-specifics have been tried as aids to this process, and found wanting. To control parkinsonism (muscular rigidity and poverty of movement, tremor, drooling, upward rolling of the eyes and eyeclosure), drugs of the belladonna series are used. The alleged therapeutic value of acriflavine, trypan blue, pyridoxine, and fever therapy has not been confirmed. Hall (1943) cited the case of a woman who had difficulty in chewing and swallowing her food except at about two o'clock in the morning, and pointed out that this relief of inhibition, or whatever it may be, during the night hours or when half-awake is not uncommon in the automatic acts such as speech and gait. He also pointed out that in cases of disturbance in gait self-confidence is often restored by taking lightly hold of somebody's arm or by the use of some type of brace for its psychical effect. Hall said that in his experience least effect from the belladonna drugs is obtained in attempts to control the eye symptoms, which is unfortunate because sometimes they are the only disability preventing employment. In some of his worst cases of drooling which had not been checked by the belladonna drugs he succeeded with deep x-ray therapy over the salivary glands. It seems to me that surgical attempts to interrupt nervous pathways are still in the early experimental stage since there does not seem to be as yet agreement between neurologists, neurophysiologists and neurosurgeons as to the exact connecting links between the muscles and the brain at which interruption might most suitably be attempted.

The belladonna drugs are used as follows:

(*a*) Atropine sulfate is started at 1/80 grain (0.75 mg.) thrice daily and increased by 1/120 grain (0.5 mg.) twice daily until maximal therapeutic effects, or toxic disturbances, are obtained. In some instances doses of $\frac{1}{6}$ to $\frac{1}{3}$ grain (10–20 mg.) daily are given for many months; this was the average optimal, indeed, in Hall's (1937) series, and in one of his cases 54 mg. was required and tolerated. Jewett *et al.* (1938) also used high dosage satisfactorily. Schlezinger and Alpers (1941) used a synthetic atropine-like drug, syntropan, and thought it of definite value: maximum benefit was experienced when the total daily dosage of 2.4 Gm. could be tolerated.

(*b*) Bulgarian belladonna: for some years there has been an impression on the Continent that a white wine decoction of Bulgarian belladonna was superior for this purpose to atropine. In England, the findings of Hill (1938) and

of Alcock and Carmichael (1938) were conflicting. In the United States, Neal and Dillenberg (1940), making trial of the decoction under the auspices of the Matheson Commission for Encephalitis Research in New York City, obtained results in approximately 100 patients which they described as far superior to those obtained with any other form of symptomatic treatment. The decoction having been found to deteriorate upon standing, a tablet has been prepared and is available under the name "bellabulgara." It was found necessary to use sufficient dosage (which must be separately determined in each patient) to cause marked dryness of the throat and blurring of vision and then, when these symptoms subside after a few days on this dose, to push up to the point of causing really toxic symptoms, such as gastro-intestinal and urinary disturbances, headache and dizziness. Fabing and Zeligs (1941) found a white wine extract of U.S.P. belladonna root fully as effective as the Bulgarian preparation; the point seems to be that white wine extracts yield products qualitatively different from those obtained by hydroalcoholic extraction (tinctures)—*if* they do; I think some time must pass before we can be sure of this.

(*c*) Scopolamine hydrobromide (hyoscine), 1/200 to 1/100 grain (0.0003–0.0006 Gm.) several times daily.

(*d*) Stramonium: the powdered leaves (in capsules or pills) are given at one- or two-hour intervals until good effect is obtained, after which a maintenance dose is employed. In the beginning 15 to 30 grains (1–2 Gm.) may be distributed during the twenty-four hours; a maintenance dose of 8 grains (0.5 Gm.) has been found to be well tolerated for many months. Of the tincture, 60 to 90 minims (4–6 cc.) three times daily is generally effective.

(*e*) Combined alkaloids: an alkaloid mixture consisting of 90.2 per cent hyoscyamine hydrobromide, 7.4 per cent atropine sulfate and 2.4 per cent scopolamine hydrobromide was reported by Vollmer (1942) to be more effective than the other agents.

Hurst (1934) found that he could continue the use of a drug of the above group in some patients after there was complaint of dryness of the mouth and paralysis of accommodation by combining with it 1/10 grain (0.006 Gm.) pilocarpine nitrate; some of his patients received doses as large as 2/5 grain (0.024 Gm.). Solomon *et al.* (1937) found benzedrine sulfate (amphetamine) of some adjuvant value, especially when symptoms of drowsiness and lack of energy predominate; Finkelman and Shapiro (1937), Matthews (1938), and Davis and Stewart (1938) had similar experiences.

PROPHYLAXIS

Slesinger (1936), in the outbreak of St. Louis type encephalitis in Windber, Pa., felt that convalescent serum was definitely worth employing in prophylaxis, but this impression seems to have been based solely upon the fact that 2 cases occurred in the exposed hospital personnel prior to the administration of 5 cc. of the serum to 7 of the remaining personnel and no new cases thereafter.

A bivalent vaccine against equine encephalomyelitis of both the eastern and western types has been extensively employed in horses and mules; it is said (Bulletin of the U. S. Army Medical Department, March, 1944) that since inauguration of the annual vaccination of all horses and mules in the U. S. Army in 1939 only one case had occurred and that in an animal that came down with the eastern type after having been immunized only against the western type. These vaccines are now commercially available for human use and it is thought that they will probably be very effective in man. However,

since both morbidity and mortality have been low in most outbreaks of the disease in the human, Hammon (1943) said that mass immunization programs with this vaccine are not indicated, though he felt that the agent should be used in selected groups of heavily exposed persons. Vaccines against the St. Louis and Japanese B viruses have also been developed, and Sabin (1943) said that tests on human volunteers indicated that two doses of 2 cc. given three days apart could be administered without fear of local or systemic reactions and that this amount of vaccine contained enough antigen to stimulate the development of neutralizing antibodies in about 50 per cent of adults. He felt that in the face of a very severe developing epidemic of one or other of these two types of encephalitis it might be desirable to test the effectiveness of these vaccines in protecting human beings. The Russians seem to have developed a fairly satisfactory vaccine against their spring-summer tick-borne encephalitis; Smorodintsev (1944) reported that only 2 out of 925 vaccinated personnel came down with the disease whereas 27 were afflicted with it among 1185 unvaccinated controls.

EPIDEMIC PLEURODYNIA

(*Devil's Grip, Epidemic Myalgia, Bornholm Disease, Bamle Disease*)

Epidemic pleurodynia is an acute infectious disease characterized by sudden onset with excruciating muscular pain at the site of the attachment of the diaphragm to the anterior thoracic wall on either side, or in the epigastrium; marked increase in rate and decrease in amplitude of respirations; several degrees of fever; and rather constant headache, but rarely pain elsewhere. The aching muscles are sometimes tender and noticeably swollen. The pain usually leaves within twenty-four hours as suddenly as it came; the fever also subsides, the patient breaks out into a sweat and, being greatly relieved, falls into a refreshing sleep. There is often an attack of lessened severity one or two days to a week later, but a third seizure is rare. In an epidemic in Brooklyn, New York, involving 171 cases, Howard *et al.* (1943) reported that five of the adults had manifested apathy and photophobia and experienced vertigo as well as headache, and practically all of the infants in this outbreak had convulsions. Frank pleurisy, heretofore considered a rather rare complication, was encountered three times in the Brooklyn series, and there was an unusually high incidence of pharyngitis also. Muscular tenderness and swelling often persist for several weeks after subsidence of the acute attack; Howard (1938) noted that in some instances defecation is more or less frustrated for a time by the excruciating pain. Children seem to be more susceptible to the disease than adults.

Rimpau (1938) said that this entity was first described by the Dane, Hannaeus, in 1735, and all students of the subject agree that it was observed in Iceland in 1856 and again in 1863, then in Norway in 1872. Its first appearance in America was apparently in 1888, at which time Dabney described it without knowledge of Finsen's prior notations on the Scandinavian cases. Since then outbreaks have been recorded in England (where Pickles' graphic accounts show how puzzling the attacks may be unless this entity is borne in mind), Denmark (Sylvest's monograph, now available in English, is very ex-

cellent), Sweden, Finland, Germany, Portugal, New Zealand, Switzerland and numerous parts of the United States. The most recent bacteriologic studies, those of MacDonald *et al.* (1937), revealed nothing regarding the etiologic agent. Small found a plasmodium in the blood but no one else has succeeded in doing so. Since this is a summer disease and often attacks several members of a family at about the same time, it has been looked upon as atypical dengue or at any rate as being mosquito borne, but these surmises remain uncorroborated. It is likely that the disease spreads by direct contact but nothing more exact than this is known with regard to its epidemiology.

THERAPY

The patient wishes to lie undisturbed, as every movement of the trunk causes an agonizing twinge of pain. In a few cases, hot or cold applications are a sufficient analgesic measure, but usually some drug has to be used in addition. Acetanilid, 3 grains (0.2 Gm.), acetphenetidin (phenacetin), 5 grains (0.3 Gm.), antipyrine (phenazone, B.P.), 5 grains (0.3 Gm.), acetylsalicylic acid (aspirin), 10 grains (0.6 Gm.), have all been used at three- to four-hour intervals. In the more severe cases these drugs are not at all effective and opiates must be resorted to, but before giving morphine or dilaudid one might try a few doses of the following combination, cutting the amounts in half for children under fifteen years:

℞ Codeine phosphate
Phenobarbital
Extract hyoscyamus..... āā gr. vj 0.4
Acetanilid..... gr. xxxvj 2.3
Divide into 12 capsules.
Label: 1 capsule every three hours.

Small stated that the prompt exhibition of quinine sulfate, in doses of 3 to 5 grains (0.18–0.3 Gm.) every two hours until 20 to 30 grains (1.2–1.8 Gm.) have been given, appears to terminate the disease specifically and to prevent the recurrence of paroxysms. He directed that half this daily dosage should be maintained for a period of one week after the temperature has become normal. I have found no other record of this felicitous use of the drug.

EPIDEMIC SORE THROAT

(*Septic Sore Throat, "Glandular Fever"*)

This is the type of sore throat which appears in the winter and spring in explosive epidemics and is in most instances directly traceable to the ingestion of milk, or milk products, which are contaminated with *Streptococcus epidemicus*. The symptoms in the individual are sudden onset of chilliness, malaise, headache and vague body pains, high rise of temperature and swelling of the cervical lymphatic glands. The pharynx is extremely painful, swollen, congested, and usually shows a diffuse, thin grayish exudate; sometimes there is a punctate rash on the palate; in some instances (Tilley and McKenzie, 1935) the larynx is chiefly affected. The complications are those most frequently seen in scarlet fever also, *i.e.*, peritonsillar and retropharyngeal abscess, cellulitis of the neck, tonsillitis, otitis media and mastoiditis, nephritis

and arthritis; indeed, it is nowadays accepted by most observers that streptococcal sore throat and full-blown scarlet fever are very closely related entities. In a number of milk-borne epidemics of streptococcal infection in New York State, Stebbins (1943) classified the individual outbreaks as scarlet fever or septic sore throat depending upon the frequency of typical scarlatinal rashes, since patients who developed a rash were clinically indistinguishable from sporadic cases of scarlet fever, while those in which no rash was observed were clinically indistinguishable from cases usually diagnosed as tonsillitis. In most cases the symptoms subside in a few days, but the patient remains prostrated for some time longer. A recurrence several days after resuming activity is not uncommon.

THERAPY

It has not been shown that the sulfonamides are effective in lessening the severity or shortening the duration of this infection but they are nevertheless being used nowadays in practically every type of sore throat in the hope of reducing the incidence of serious complications; I have not seen the record of any extensive controlled study in which it was shown that this desideratum was achieved, but that does not mean of course that good results are not being obtained. Most attempts at specific therapy with antistreptococcal serums or vaccines have failed, but Camps and Wood (1936), in a British epidemic of about 1600 cases, felt that the intramuscular injection of scarlatinal antitoxin many times shortened the course and lessened the complications and that complicating arthritis was definitely improved by it. Dobell's solution (Compound Solution of Sodium Borate, N.F.) diluted one half with water, or Alkaline Aromatic Solution, N.F. (which much resembles the nostrum "glycothymoline," so beloved of the lay public—*and* the profession?), is usually very gratefully received by the patient when used as a spray. Cold packs about the throat often give much relief. Otherwise the symptomatic handling of these cases does not differ markedly from that of the common cold, influenza, or scarlet fever, all of which are separately discussed elsewhere in the book. Suppurative complications in the neck require surgical treatment.

ERYSIPELAS

Erysipelas is an acute disease characterized by a spreading erythematous skin lesion plus more or less profound constitutional symptoms. It is known to be caused by several strains of the hemolytic streptococcus, perhaps but not certainly that particular one known as *Streptococcus erysipelatis;* the organism is thought by some to enter a preexisting skin abrasion in all instances, though history of antecedent injury is not obtainable in most cases. Mucous membrane cases are rare. Active adults in the middle decades, persons who have recently undergone a major operation and women in the puerperium are the most frequent victims, though individuals of any age and either sex are liable to the disease. Some persons manifest an especial susceptibility (perhaps because of some nasal or other focus of infection or because the skin remains hypersensitive to the organism) and have many attacks during their lives. In adults the face is perhaps more often affected than any other portion of the body, but in the newborn the infection often begins in the umbilical region, at the site

of a forceps abrasion or an impetiginous lesion, or commonly in the diaper region; in later infancy it more commonly begins from an otitis media, acute rhinopharyngitis, or impetigo. Before the institution of sulfonamide therapy mortality seemed to range between 10 and 20 per cent in young adults but was much higher in individuals over fifty; Brennemann (1941) said that it was 76 per cent for children below one month and 46 per cent for children up to two years of age.

The onset is sudden with high rise of temperature, malaise, headache, sometimes vomiting and not infrequently delirium. Bruce and Chalkley (1943) said that in infants, although the temperature may rise to 106° F. (41.1° C.), convulsions seldom occur. The skin lesion appears coincidentally with the constitutional symptoms. The typical lesion is a red, swollen area with sharply demarcated and elevated border; small, flamelike extensions along the lymphatic channels are usually seen beyond this border. There is often a scattering of small vesicles throughout the affected area. The lesion spreads rapidly, and as it extends the earlier affected portions subside and desquamate. Sometimes localized abscesses, or necrotizing ulcers from secondary infection, form in the border, or the whole region may be undermined with pus. Pain, often quite severe, is of the burning order. The swelling in typical cases is very considerable. Fever usually persists for two or three days and then falls by lysis or crisis, usually several days before the complete subsidence of the skin symptoms. However, one cannot make any definite prediction in regard to the course of the fever, and indeed the whole clinical picture may persist, with relapse after relapse, for several weeks instead of the usual duration of four to eight days.

This disease, though contagious and serious enough, does not tend to become epidemic and has not been given great attention by medical writers through the ages. Hippocrates did not describe it, though Galen mistakenly accepted his account of anthrax as applying to erysipelas. It is extremely likely that some of the cases of ergotism, which were so numerous during the Middle Ages, were really this disease. Fehleisen showed the streptococcus to be causative in 1883 Tunnicliff definitely separated the streptococci of scarlet fever and erysipelas in the period 1920 to 1927.

THERAPY

Sulfonamides.—There can be no doubt that the drugs of this group have supplanted every other agent as the method of choice, sulfanilamide still being the preferred drug. There are numerous careful studies available, of which the following are characteristic. Hoyne *et al.* (1939) reduced erysipelas mortality in Cook County Hospital to 2.46 per cent including all types and age groups and even deaths which occurred shortly after admission. Nelson *et al.* (1939) compared the results at Bellevue Hospital as follows: in 406 patients treated with erysipelas antitoxin the mortality for adults was 9.2 per cent, for children 37.5; in the group of 344 sulfonamide-treated cases these figures were respectively 1.5 and 12.9 per cent; Snodgrass *et al.* (1938), in England, reported a total mortality rate of only 2.06 per cent in 242 patients. Typical is the experience of Foley and Yasuna (1940), in Boston, who reported that in their 80 sulfonamide-treated patients a return to normal temperature occurred almost two days earlier than in the 80 control cases, the hospital stay was shortened three days, complications occurred only half as frequently. The lesion ceases to spread within forty-eight hours in the experience of most

observers but begins to change its appearance in half this time; in no instance in the 165 consecutive cases of Shank *et al.* (1941) did the lesion continue to spread after thirty-six hours on chemotherapy. In Foley and Yasuna's series the average dose of sulfonamide employed during the first twenty-four hours was 7 to 8 Gm. and 5 or 6 Gm. were given each day thereafter. In the infants treated by Bruce and Chalkley (1943) the best dosage seemed to be $1\frac{1}{2}$ grains per pound (0.2 Gm. per kilogram) of body weight per day divided into 6 or 8 equal doses, the first dose being twice the amount of the following doses; dosage was continued for three or four days after the temperature returned to normal.

Ultraviolet Irradiation.—The studies of Ude and Platou (1930) and of Titus (1933) introduced the American and British worlds to ultraviolet irradiation in erysipelas, which had been having good reports on the Continent for about ten years previously. Comparative series of cases showed the method to be very likely more effective than serum therapy. Lavender and Goldman (1935), equally with Titus, stressed the need for boldness in dosage; their patients received an average of 3 exposures, twenty-four hours apart, of about 18.8 erythema doses per exposure. The involved area and the region 1 to 2 inches surrounding it are treated. In infants, Nightingale and Starr (1934) gave 3 exposures of 1.5 erythema doses on successive days regardless of the clinical course; Willis (1939) gave 3 daily exposures of 6 erythema doses with the light at 10 inches and making no allowance for infants or blondes.

Ultraviolet irradiation has settled down into second place to the sulfonamides as the method of choice, but Bruce and Chalkley (1943) went so far as to state that the use of ultraviolet rays is not necessary.

Antitoxin (Serum) Therapy.—After its introduction by Birkhaug in 1926 and original extensive trial at Bellevue Hospital, the specific erysipelas antistreptococcic serum was widely used and seemed to justify the early hopes that were felt for it. It is expensive, however, and carries with it the threat of serum sickness and immediate or delayed reaction to horse serum, which makes precarious the position of any serum that does not give almost perfect results. Fox (1937), analyzing his 378 cases, found that mild and moderate clinical types responded well to any of the empirical measures, and therefore felt that serum should be employed only in severe cases. Symmers and Lewis, of Bellevue Hospital, recommended the introduction intramuscularly of 25 cc. at the moment of the patient's admission, repeating usually at intervals of twenty-four hours until the erysipelatous blush disappeared, the edema was dissipated and the temperature became normal. Often 2 or 3 injections were necessary, occasionally more. In infants the dose was 10 cc.

That serum therapy will hold any place for itself in competition with the sulfonamides is extremely doubtful; Toomey (1938) very trenchantly made this point in effect when he reported a total mortality rate of 13 per cent in his large series of serum-treated cases as against 15.5 in the untreated cases and pointed out that it is not necessary to use a control series to show the benefits of antitoxin in diphtheria and of the sulfonamides in erysipelas. Bruce and Chalkley (1943), discussing the treatment of erysipelas in infants, stated that the use of the antitoxic serum is no longer necessary.

Miscellaneous General Measures.—Types of therapy which formerly had their advocates and have now been practically abandoned in favor of the sulfonamides are convalescent serum, blood transfusion, foreign protein therapy, tincture of ferric chloride.

Local Measures.—The application of cold compresses is often soothing. Sometimes the making of the compress with saturated solution of magnesium sulfate, instead of plain water, affords relief from the burning pain, but this treatment apparently enhances the development of abscesses. Hallay powders the diseased area with sodium bicarbonate. From 10 to 20 per cent of ichthyol in an ointment in some cases exerts an analgesic effect. Hydrous wool fat (lanolin) should be used as a base because its adhesiveness permits of long application. Fox (1937) preferred continuous wet compresses with 1:1000 Burow's solution to all other local applications. Painting the skin beyond the border of the lesion with tincture of iodine, or a strong solution of silver nitrate, is said sometimes to stop the advance of the process. Eldridge applied a 5 per cent aqueous solution of mercurochrome to the whole affected area once daily until the eruption was well on its way toward subsidence; Adams has used brilliant green. Some men experienced in the handling of many cases of erysipelas object to a number of the above measures because they obscure the true appearance of the lesion. Avata and Woodyatt introduced the practice of circumscribing the diseased area with a stripe of nonflexible collodion, ½ inch wide and ½ to 1 inch in advance of the line of induration. As it dries, the stripe is painted over repeatedly to make a deeply constricted and unbroken furrow; very good results are sometimes reported with this method, but nowadays the sulfonamides effect such early changes in the lesions that this method of attack is only rarely employed.

Prevention of Recurrent Attacks.—As a result of the investigations of Amoss, one of the pharmaceutical manufacturing houses has made available extracts of seven strains of streptococci for use in skin testing to determine by allergic reaction which should be used for desensitization in the individual case. The area of previous involvement and a corresponding area on the other side of the body are injected intracutaneously with 0.05 cc. The previously involved area usually shows more marked reaction to one of the strains and this one is then selected for the desensitization attempt; beginning with 0.1 cc. increasing doses are injected at five-day intervals until 1 cc. is given. After 6 of the 1-cc. doses skin tests are repeated to determine the state of susceptibility. Amoss (1931–1936) stated that in 38 cases thus treated he had stopped the attacks but that in 2 there were recurrences after long intervals, 1 at eight and 1 at nine years after desensitization. The injections were repeated and no further attacks occurred. I have seen no recent reports of the employment of this method.

ERYSIPELOID

Erysipeloid is a disease which has been shown to be caused by a modified form of the *Erysipelothrix rhusiopathiae* of swine erysipelas, a bacillus that is apparently either pathogenic or saprophytic throughout the animal kingdom. In America most of the cases have been reported from the Atlantic seaboard, with a few from the Great Lakes region, and have nearly all been in fish handlers and in handlers of the flesh of swine in packing houses. But the exceptions exhibit a wide gamut of possibilities, such as injury of the hand in the bed of a dried creek, skinning a rabbit, carrying an opossum by the tail! Lawson and Stinnett (1933) had under observation 210 cases which occurred within

one year in a factory making buttons from cattle bones, and Gross (1940) reported 13 cases among veterinary students, with horse cadavers established as at least one source of infection. The disease is characterized by early pain, followed by the appearance, after an incubation period of two to four days, of a sharply circumscribed, quadrangular, bluish-red lesion on the skin at the site of the infecting injury, the inflammation often gradually spreading to involve a large part of the hand. Sometimes it clears up in one finger but goes down another and may then even return to the site originally infected. There is local pain and swelling but the latter rarely extends above the wrist. Constitutional symptoms are mild, but cellulitis, lymphangitis, and lymphadenopathy may occur, and the appearance of a diffuse erythema accompanied by the symptoms of sepsis has been reported. The majority of cases run a self-limited course of about three weeks, but in Germany, and recently in America (Klauder, 1938), there has been observed a chronic form of the disease which is characterized by polyarthritis; indeed, in America some of the cases have been observed to start up again in previously uninvolved areas after a short period of apparent cure. Russell and Lamb (1940) and Klauder *et al.* (1943) each reported bacterial endocarditis caused by *E. rhusiopathiae* as a fatal complication in one case; such observations had previously been made in Germany. In the fatal case of Klauder *et al.* the character and distribution of the rash resembled the purpuric and petechial eruption that is seen in extrameningeal meningococcic infection; these observers felt that an increase in the monocytes was a point of diagnostic significance. In the severe fatal form of the disease in swine the ears often become swollen, purplish red and obviously painful, and this occurrence has been observed in man also (Klauder, 1944).

THERAPY

The only distinctive treatment which has been developed consists in the administration of immune serum which is available from several of the pharmaceutical manufacturing houses. However, the incidence of serum sickness has been particularly high after the systemic use of this serum. In Klauder's (1938) report he stated his belief that the serum is indicated only if the infection persists for a month, if it progresses rapidly, or if arthritic symptoms are conspicuous. For treatment of the most severe cases Klauder *et al.* (1943) recommended that 100 cc. be given intravenously every twelve hours for the first 4 to 6 injections, further treatment depending upon the clinical results. The sulfonamides were found to be without effect by Klauder and Rule (1944). Heilman and Herrell (1944) found penicillin highly effective in experimental infections in mice and felt it reasonable to assume that it would prove effective in the treatment of the disease in man.

Of course a wide variety of locally applied treatments have been tried. Klauder felt that splinting the hand is to be preferred to the use of a sling and favored the application of constant wet dressings of 12 per cent ichthammol (ichthyol) in alcohol. He further thought that repeated erythema doses of ultraviolet light might be helpful but admitted difficulty in evaluating treatment since the infection usually apparently runs a self-limited course. Griswold and Bowen (1944) applied solid carbon dioxide with firm pressure to the lesions for two to four seconds, several centimeters of the apparently uninvolved tissue peripheral to the area of infection being also similarly treated. The treatments were repeated at intervals of one or two days, depending upon the presence of vesiculation or bullae from the previous application, and it was said to be

rarely necessary to use more than three applications. The discomfort following the application of solid carbon dioxide was controlled by the use of salicylates internally. Fifteen cases were treated by this type of cryotherapy with no loss of time from work in any case beyond the first day of treatment and with an average duration of infection of four and two-thirds days and no duration longer than nine days in any instance.

FOOT-AND-MOUTH DISEASE

Foot-and-mouth disease is a highly contagious malady of domestic cloven-footed animals; Hull (1941) said that dogs, cats and poultry may occasionally become infected. The guinea pig is the animal preferred for the study of the disease in the laboratory. The malady is caused by a filtrable virus which is sometimes transmitted to man through the medium of infected milk or milk products or contact with diseased animals. The human cases are rare and transmission from man to man doubtful; indeed the great resistance in man was clearly shown in 1908 when smallpox virus vaccine infected with foot-and-mouth disease virus was widely distributed in the United States without the occurrence of a single human case. Among livestock the disease is widespread in Europe, South America and other parts of the world; the United States has several times experienced severe epidemics, which have been stamped out by mass killing, immediate burial and rigid quarantine. Studies in England have shown that dressed carcasses of infected animals may retain their infectivity even after ten weeks of refrigeration.

That great man, Girolamo Fracastoro (1484–1553)—who wrote the first complete description of syphilis, foresaw clearly the modern conception of the bacterial causation of disease and performed many other feats of original genius—described the first recorded epidemic of foot-and-mouth disease. And, indeed, since his time there has not been a great deal written upon it in the strictly medical press. In 1898, Loeffler and Frosch proved experimentally that the malady is caused by a filtrable virus; in fact, this was the first disease proved to be caused by a filtrable agent. I give Clough's summary of the symptoms: "A mild febrile infectious disease, characterized by the appearance of an erythema and a superficial vesicular eruption over the mucous membrane of the mouth and on the skin of the hands and feet; by salivation, by swelling, burning and paresthesia of the affected parts, with subsequent desquamation; and by healing of the ulcers without scar formation." Diagnosis is accomplished by inoculating blister fluid into the scarified skin of a guinea-pig's foot.

THERAPY

Treatment consists in the use of antiseptic mouth washes such as 1:2000 potassium permanganate. The silver nitrate stick may be applied to the ulcers just as in the treatment of canker sores. I imagine the lotion of calamine and zinc (see Index) would be soothing when applied to the lesions on the body surface, and an ointment containing about 0.5 per cent holocaine (phenacaine) would allay mucous membrane pain. Very little has been written about the treatment of the disease; all attempts to influence its course by the intravenous introduction of dyes or other antiseptic substances have usually not

succeeded, but von Scheitz (1934) stressed the beneficial effects of neoarsphenamine. I have seen no account of the successful employment of a sulfonamide or of penicillin.

GANGOSA

(See *Yaws*)

GAS GANGRENE

(*Clostridial Myositis*)

Gas gangrene is caused by one or several clostridia lorganisms, the chief of which are *Clostridium welchii*, *Cl. oedematiens* (*Cl. novyi*), and *Cl. septicum* (*vibrion septique*), the pathogenicity of these organisms being associated with the elaboration of toxins. These bacilli are normally present in the feces of animals and man and hence are widely distributed in soil throughout the world; they have also been recovered from room sweepings, glass syringes and from numerous other sources. They have been recovered from the apparently normal organs of the genito-urinary tract, from surgically extirpated gallbladders and from wounds in which there was no clinical evidence of gas bacillus infection. However, under certain abnormal environmental conditions the organisms take on pathogenic propensities and give rise to a toxemia with extremely high mortality. In ordinary civilian practice these conditions are encountered most frequently in traumatic surgical cases but such occurrences are also not unknown in intestinal perforation, intestinal obstruction, gangrenous appendicitis, or in surgical conditions of the genito-urinary tract. But first and foremost gas gangrene is a complication of wounds received in battle. The deep wound from which air is excluded and in which there is partially devitalized tissue, especially muscle, is the site in which these organisms grow fast; the presence of foreign bodies or of other bacterial toxins or anything tending to promote necrosis aids establishment of *Cl. welchii*. Once the focus is established the infection may remain localized in the wound or it may spread into a single muscle or a group of muscles or involve a large segment of the limb, or indeed there may be a general spread in all directions in extremely severe cases. Organs with the most abundant blood supply are the least likely to be affected. Experience in War II abundantly confirmed the earlier impression that gas bacillus infections are very uncommon about the head and neck and occur with greatest frequency in the buttock, thigh and leg, the infection in the buttock being especially dangerous. It is ordinarily considered that when gas gangrene has set in the wound will quickly take on a distinctive appearance, becoming swollen with a serosanguineous fluid having a characteristic mousy odor and taking on a yellowish hue with purple and green patches; it has been thought too that palpation of the wound and even of the surrounding tissues at some distance removed from it elicits crepitation as a sign of the presence of gas in the tissues. However, MacLennan (1944) pointed out, as a result of extensive experience in the Mediterranean area in War II, that the presence of gas is a variable and in itself a valueless criterion of clostridial infection of

muscle, and that the constant features are pain, swelling, and toxemia; of these pain, being the first to appear, is of the greatest significance. In fact MacLennan felt it not too much to say that, in wartime, the possibility of an anaerobic myositis must always be borne in mind when there is a sudden and unexplained onset or increase of pain in an infected wound. The rise in temperature is often only moderate but the greater proportionate increase in pulse rate is a more valuable index to the degree of the toxemia. In MacLennan's 44 cases the incubation period varied from five hours to twenty-nine days, but if one excludes the exceptional case of twenty-nine days the average of the other 43 cases was 1.6 days; no correlation was discerned between the length of the incubation and the clinical picture, the degree and type of injury, the nature of the bacterial flora, or the ultimate outcome.

THERAPY

In MacLennan's series of cases, above cited, the mortality was only 30 per cent and success in keeping it so low was attributed to accurate diagnosis, good surgery and intensive serotherapy; all else was considered to be of secondary importance.

Surgery.—What constitutes good surgery in a given case will of course depend upon the condition of the patient and obviously cannot be described by me. At times apparently it may suffice to lay the affected area wide open, at other times complete excision of the wound and removal of the injured or infected tissues seem necessary even though this will lead to the sacrifice of a whole group of muscles; in many cases high guillotine amputation has to be resorted to.

Serum (Antitoxin).—Since the rationale of the administration of antitoxin is to neutralize the circulating toxins, the antiserum must be given in gas gangrene cases as long as toxemia persists. The first dose should be given as soon as possible, not delaying until after operation, and should be not less than 50,000 units of the polyvalent antitoxin and perhaps as high as 100,000 units or more in fulminating cases; doses in amounts which seem indicated should then be repeated at four to six hours until a decrease in pulse rate indicates a satisfactorily diminishing toxemia. All administration should be intravenous, but MacLennan and MacFarlane (1944) found it preferable to give the antitoxin in small volume rather than to spread out the dose over many hours in an intravenous drip, this being especially important in the early stages of the disease. It is important to remember that even when the main source of infection has been removed by excision, the production of toxins may continue in small inaccessible remnants of necrotic tissue and that therefore the indication for the continued use of serum may persist.

Sulfonamides.—In the early studies of sulfonamides in experimental infections it was found that the survival rate of animals was very little affected by orally administered sulfonamides, but when the agent was applied locally to the infected wound considerable success was attained. Nowadays under field conditions it is not possible accurately to assess the part played by sulfonamides in the control of gas gangrene infection because they are used routinely, both locally and systemically, in all cases. MacLennan (1944) believed that it would certainly be undesirable to discontinue the use of the sulfonamides though he felt that their action was only adjuvant to that of good surgery and ample use of antitoxin. He made the further point that in very toxic cases administration should be by intravenous drip.

Penicillin.—In a discussion of gas gangrene in which notable British authorities participated, Jeffrey (1944) said that he believed penicillin to be the chemotherapeutic agent of choice since it inhibits the clostridium more surely than do the sulfonamides; given parenterally he felt that it should prevent multiplication of the infecting organisms and the spread of infection but that it would not prevent absorption of toxins in gangrenous muscle and that for this reason its employment remains auxiliary to and in no way supersedes the other two essentials of treatment, *i.e.*, surgery and the effective employment of antitoxin. Jeffrey and Thomson (1944) felt it wise to have both the antitoxin and penicillin circulating in the blood before the operative procedures are undertaken. In the report on the use of penicillin in war wounds in the Mediterranean area in War II, made to the British War Office and Medical Research Council by Florey and Cairns at the end of 1943, the position was taken that fulminating cases of gas gangrene with profound toxemia are not likely to be saved by penicillin but that it may be expected that the agent will play an important part in prevention. This was essentially the position taken by Herrell *et al.* (1944) in discussing their experience with a small number of cases at the Mayo Clinic.

Transfusion.—In gas bacillus infections there is usually profuse serous oozing from the wound site and a profound and progressive toxemia manifesting itself principally by circulatory failure and collapse—all of this often superimposed upon the hemorrhage and shock associated with the original wound. It is therefore easy to agree with MacLennan (1944) who said that it would be hard to exaggerate the importance of transfusion therapy in gas gangrene. Of his 44 cases, 41 were given blood, plasma, or glucose-saline, usually in very large amounts, and had the other 3 patients lived long enough, they too would doubtless have received this treatment. Almost but not quite invariably whole blood has proved to be more valuable than either plasma or serum for infusion. It may be well to warn the reader against an error into which he may fall, namely, that of persisting in the administration of blood or plasma until extravagantly large amounts have been given in the belief that it is primarily shock rather than toxemia which is sapping the patient's life away.

Proflavine and Zinc Peroxide.—Both of these agents have a good record in experimental gas gangrene infection but at the time of writing neither of them has had sufficient trial in the field to warrant an attempt at comparison between them and the sulfonamides and penicillin.

X-Ray.—In a review of all aspects of gas gangrene, Reed and Orr (1943) stated that the results obtained by those who advocate the use of x-ray therapy are far from convincing. Upon the request of the Surgeon General of the United States Army, in 1944, the National Research Council through its Sub-Committee on Radiology of the Division of Medical Sciences considered the matter and delivered the opinion that up to the present time the effectiveness of x-ray in the treatment of gas gangrene has not been established.

PROPHYLAXIS

It is considered highly advisable to administer at least 20,000 units of polyvalent antitoxin for prophylactic purposes to individuals who have received severe wounds of the buttock, thigh or shoulder, or compound fractures of the femur, or penetrating wounds in which primary surgical treatment has been delayed more than twenty-four hours. I do not have before me any statistics

of the results of such prophylactic procedure in the American Army, but MacLennan and MacFarlane (1944) reported that in the British Eighth Army in Italy the mean incubation period of the disease was sixty-eight hours in 34 patients who received prophylactic antitoxin whereas in 41 patients who had not received antitoxin (presumably because they were not considered likely to develop gas gangrene) the mean incubation period was thirty-three hours.

GERMAN MEASLES

(See *Measles and German Measles*)

GLANDERS

(*Farcy, Malleus*)

Glanders is an infectious disease of horses, mules and donkeys. It is caused by *Malleomyces mallei*, and is communicable to man. The cases in man, which are fortunately rare for the disease is usually fatal, are nearly all contracted directly from a diseased animal, though the danger of laboratory infection with the organism is very great, as was dolefully reemphasized in Prague, in 1924, when three well-known scientists succumbed to the disease within a brief period. The outbreak which they were investigating claimed in all 7 deaths (in 7 cases), all deriving from one infected horse. Upon the other hand man seems to be quite resistant to infection under ordinary conditions. Hull (1941) cited an instance in a road construction camp in Illinois in which 19 horses died of the disease and some 50 more infected animals were killed but among the 600 or 700 men in camp who had been in more or less close contact with the animals only 1 case developed. Acute glanders in man may begin with symptoms indicative of almost any of the other infectious diseases, which makes early diagnosis very difficult; however, Symmers says: "The occurrence of symptoms of an acute infective disease in an individual who comes in contact with horses and who presents multiple abscesses in the skin or in the mucous membrane of the nose, with deep-seated pain or tenderness, indicative of abscesses in muscle tissues, tendon sheaths, fascia or periosteum, with or without joint symptoms, should suggest the diagnosis of glanders in spite of the extreme rarity of the disease, and confirmation should be sought in isolation of the causative bacillus and guinea-pig inoculation." There is also a chronic form of the disease which must be differentiated (Burgess, 1936) from granuloma inguinale, lymphogranuloma inguinale, tuberculosis of the skin, syphilis and mycotic and yeast infections; Hull (1941) cited a case admitted to hospital for pneumonia and diagnosed as glanders only several weeks later after a positive laboratory examination, and Panja and Chatterjee (1943) described a case which had been mistaken for smallpox.

It is thought that the strange affliction of animals and men during the ninth to twelfth centuries, called *malum malannum* because of its recurrence in troublous years, was either anthrax or glanders. Solleysel described the trans-

mission of the disease from horse to horse in 1664. The classical monograph on the disease in man is that of Rayer, in 1837. Loeffler discovered the causative organism in 1882.

THERAPY

There is no specific treatment for glanders in man. The palliative measures directed to the relief of the general constitutional symptoms do not merit special description here; they are such as are applied in any other fulminating condition. It is said to be advisable to excise the local nodule where possible, though in an outbreak, in 1926, of 7 cases in eastern Austria, 5 terminated fatally in spite of the fact that the original focus was eliminated in each case. A grave disease, then, for which we have no remedy.

HAVERHILL FEVER

(See *Rat-bite Fever*)

HYDROPHOBIA

(See *Rabies*)

INFECTIOUS MONONUCLEOSIS

(*Glandular Fever*)

This is an infectious and probably contagious disease characterized by intermittent or remittent fever which continues for one to three or four weeks, complaints of general malaise, sweats, sore throat, often but not invariable general enlargement of the superficial lymph nodes (suppuration very rarely occurs and salivary gland involvement is rare also), frequently a palpable spleen, perhaps a rash and a mononuclear leukocytosis and reduction in the number of neutrophilic granulocytes (polymorphonuclear cells) which gives a picture somewhat resembling that of acute leukemia without the anemia and usually without the platelet reduction characteristic of the latter. Some cases with visceral glandular enlargement simulate acute appendicitis; meningitis may be suggested by the pain and spasm of the neck muscles—indeed, according to Epstein (1936), there may actually be meningeal involvement, but Contratto (1944) observed no such involvement in any of his 196 cases; other signs of central nervous system involvement have also been seen. Conjunctivitis, jaundice with or without hepatomegaly, epistaxis, hematuria, rectal bleeding, petechial and purpuric hemorrhages—these and numerous other manifestations are recorded. In fact, Bernstein (1940), in his excellent review, said that on a modest scale infectious mononucleosis may be said to resemble syphilis

in its ability to simulate other diseases; Rubenstein and Shaw (1944) found that it may readily be confused with brucellosis. Evanescent false positive serological reactions for syphilis have been reported by several observers; Moore *et al.* (1940) said this occurs in about 20 per cent of cases. Anderson and Cox (1945) reported a very unusual case following a skin abrasion on the right leg and involving the lymph nodes only of the right inguinal region. The patients are chiefly children and young adults; no sex preference has been noted but the disease is rarely encountered in Negroes; distribution is worldwide. Cases are diagnosed the year 'round but most of the epidemics have occurred in the spring and fall. The period of incubation has not yet been accurately determined, the reported extremes being one and twenty-eight days; relapses are not uncommon and the glandular and hematological changes may persist for years. The causative organism has not been determined (though the isolation of *Listerella monocytogenes* from the throat and blood by Nyfeldt, 1929, Pons and Julianelle, 1939, and Webb, 1943, is interesting), but the diagnostic value of Paul and Bunnell's laboratory test (the finding of an elevated titer of heterophile antibodies in an individual who has not recently received an injection of horse serum) is being increasingly shown as time goes on. Both Halcrow *et al.* (1943) and Contratto (1944), reporting epidemics of considerable size in England and the United States respectively, drew attention to the necessity for making repeated Paul-Bunnell tests before excluding the disease. Kaufman (1944) found the reaction usually remaining positive for two to four months and occasionally persisting as long as one year. Spingarn *et al.* (1944) found cold hemagglutinins in the serum in high titer in a small series of patients. Biopsied lymph nodes do not seem to present a uniform pathological picture, but in the only record of a case coming to autopsy that I have seen, that of Ziegler (1944), whose patient died of a ruptured spleen in the fourth week of the disease, the microscopic observations suggested that there was hepatitis, nephritis, spleenitis and pneumonitis of a characteristic and peculiar type. Most observers consider the presence in the blood smear of a certain abnormal lymphocyte called the "mononucleosis cell" as almost a pathognomonic sign; Contratto (1944) described this cell as follows: "a large mononuclear cell with a pale-staining, rather fragile-looking cytoplasm that curled over on itself and had a large nucleus."

This disease was first described by Filatow in 1886 and first definitely envisaged as an acute infectious mononucleosis by Sprunt and Evans in 1920.

THERAPY

There are no drugs or biologicals which have any specific value. The treatment is symptomatic, recovery without sequelae occurring in practically all cases; Contratto (1944) found that most of the severe manifestations could be avoided by putting the patient to bed at once. There is one report of rapid subsidence of symptoms following x-ray therapy of the tonsils in a protracted case; Lassen and Thomsen (1940) also used convalescent serum with satisfaction, but their series of cases was very small. Bernstein routinely treats the mouth as in Vincent's angina (see Index) because of the frequent complicating presence of the Vincent organisms. Nolan's (1935) list of "don'ts" based on experience in an epidemic of 220 cases is probably still good advice: (*a*) No heat or hot applications to glands. (*b*) No hot baths in the acute stages. (*c*) No rubbing, massaging, or applications in or about the cervical or inguinal glands. (*d*) No catharsis. (*e*) When convalescent, no violent exercise involving stren-

uous stress about the groin or neck. In Bernstein's experience there has been a remarkable lack of cross-infection in patients in close contact with sporadic cases but he feels that strict isolation should be effected upon the appearance of multiple infections.

INFLUENZA

This entity is distinguishable from the common cold by the fact that, though its onset is sudden with chilliness, there is invariably an aching all over the body especially in the back and legs, the temperature rises rapidly, prostration is marked and progressive, and in the beginning at least the signs of involvement of the upper respiratory tract are minimal. Epistaxis is a common early occurrence, there may be a short brassy unproductive cough, but a head cold is usually not present. There has not been general confirmation of the allegation that leukopenia occurs in influenza. Despite the severe constitutional symptoms there is no direct evidence that influenza is a generalized infection since the causative virus has not been recovered from the blood of patients. Francis (1943) concluded that, in view of the fact that significant pathological changes have not been recognized in organs other than those of the respiratory tract, the disease represents in its pathogenesis a specific injury inflicted by a virus of sharply selective affinities upon a specialized type of cell lining the respiratory tract; according to this authority it seems probable that involvement of the pulmonary tissue, which occurs in only a minority of the patients, is secondary to the destruction of bronchial epithelium in which interstitial swelling, peribronchial infiltration and the outpouring of serous fluid and mononuclear cells represent the major changes.

Since the incubation period of the disease has been thoroughly established by both accidental and purposeful infection to be only twenty-four to forty-eight hours, and in view of the fact that the course of the uncomplicated average case is amply described in the term "three day fever," the speed of development of an influenza epidemic seems to be due to the fact that persons still in the incubation stage, those who never have more than a subclinical infection, frank cases and convalescing cases all serve as sources of infection. Francis (1943) said that the virus has actually been recovered from patients in each of these stages. Thorough study of the data of numerous epidemics since 1918 has refuted the opinion that influenza most commonly affects adults, for it has been shown that the highest attack rate is in the ages below fifteen years and that thereafter a gradual decline in incidence takes place; however, in the 1918 epidemic mortality was lowest among the children in whom morbidity was high, and in the higher ages in which incidence was lowest the highest case fatality occurred, both high incidence and high case fatality characterizing the intermediate age groups. But it should be noted that what has just been said with regard to the age distribution of the disease may be taken to apply to civilized communities only, for Smillie (1943) emphasized the fact that in isolated and more primitive communities the great pandemic swept away whole populations irrespective of age.

Influenza occurs as a sporadic, epidemic, or pandemic infection. Its name is derived from the fact that during medieval times, when it was widely spread by the Crusades, it was looked upon as a cosmic or celestial influence (*influ-*

entia coeli). Greenwood (1935), the eminent statistician, is convinced that the English Sweats of the sixteenth century were outbreaks of this disease; the correlative occurrence of lethargic states was definitely noted by Fernel at that time. Influenza was common in both the new and old worlds throughout the seventeenth and eighteenth centuries, in the latter century being dubbed *influenza* by the English and *grippe* by the French. The malady was more or less epidemic throughout the nineteenth century and pandemic in 1830–1833, 1836–1837, 1847–1848, 1889–1890. The visitation of 1918–1919, estimated by Shope (1944) to have involved about 525,000,000 and killed about 21,000,000 (the death toll in the United States alone was 548,000), is well known to many readers of this book. Since the great pandemic the disease has been numerous times epidemic in various parts of the world. There is much evidence pointing to the conclusion that an attack of influenza does not bestow an immunity of very long duration, though the limits of this duration are certainly not possible to set in the present state of our knowledge. Just why the disease at times becomes pandemic and sweeps over the world as the most destructive and most devastating of all epidemic diseases remains a riddle.

Very interesting observations on the etiologic agents in influenza have been made in the years since Smith, Andrewes and Laidlaw (1933), confirmed by Francis (1934), obtained a virus pathogenic for ferrets from the throat washings of influenza patients and demonstrated the production of antibodies against this virus during convalescence. The current etiologic nomenclature is the following: (*a*) "Clinical influenza," cases from which the virus cannot be obtained; (*b*) "influenza A," cases clinically like the above but from which the virus of Smith *et al.* (there are many strains) can be obtained; and (*c*) "influenza B," cases clinically indistinguishable from the others but from which the new Lee virus, described by Francis in 1940, can be obtained. Each of these viruses has been implicated in extremely mild and in moderately severe epidemics, but of course it is only conjectural that they were the actual causal agents during the 1918 pandemic. Shope's (1939) work indicating that the virus of swine influenza, which may be a prototype of the human disease, spends a portion of its life in the earthworm revealed an attractive new field for investigation. A comparable reservoir of human epidemic influenza has not been established and possibly indeed none such exists; there is considerable evidence that the virus may be in circulation in some part of the world at all times.

THERAPY

In addition to the employment of such symptomatic measures as are discussed in Common Cold, the two clear therapeutic indications in influenza are the following:

Rest in Bed.—It was the observation of all who experienced the pandemic of 1918–1919 that mortality was much higher among those who either would not or could not go to bed at once upon the appearance of symptoms. MacNeal and Parker (1944) stressed the fact that vigorous individuals living in comfort without strain of unusual mental or physical effort often escaped altogether or experienced only a mild illness and that the wounded lying in military hospitals did not die of influenza during outbreaks characterized by high morbidity and mortality in the hospital personnel on active duty; they said that troops in rest camps largely escaped while their fellows on heavy duty fell victims to the disease. These observers cited the specific instance of a unit of the A.E.F.,

located in Dijon, in which strict rest in bed was prescribed by military order for every enlisted man immediately at the onset of any sign or symptom of influenza; not a single death occurred among these men, but among the officers of the command who were less effectively controlled by disciplinary measures, the experience was not so fortunate. Immediate and absolute bed rest then is mandatory in the treatment of influenza.

Sulfonamides.—Since by the very nature of its attack the virus of influenza lays the respiratory tract open to secondary infection with pathogenic bacteria, it would seem the part of wisdom in the present state of our knowledge to give sulfadiazine by mouth in severe cases of influenza in the attempt to prevent complications. Finland *et al.* (1942) expressed the opinion that such therapy should be employed only in patients who harbor large numbers of pathogenic staphylococci and hemolytic streptococci or when these organisms are known to be prevalent in a community, but it is my feeling that the point will not be so finely drawn in everyday practice. Of course only a large-scale study with alternate cases left untreated as controls would ever be able scientifically to assay the efficacy of sulfonamide therapy here.

PROPHYLAXIS

Vaccines.—During the epidemic of influenza A which occurred in November and December in 1943, a Special Commission on Influenza from the Office of the Surgeon General, U. S. Army, with Dr. Thomas Francis, Jr., as director, undertook to carry out a controlled clinical trial of the prophylactic efficacy of a concentrated, inactivated vaccine containing the viruses of influenza types A and B, preceding studies having shown that a vaccine similarly prepared was capable of furnishing definite protection against experimental induction of influenza A or B in man (Francis *et al.* and Salk *et al.*, 1944). The study involved approximately 12,500 men in nine universities in different parts of the United States; in most instances the men were housed as large groups in dormitories and the proportion of them lost from the study was extremely low. Vaccination with 1 cc. of the material given subcutaneously was carried out at different times in the various units but in the main was completed by the middle of November. After the group had been vaccinated new arrivals were not taken into the study. The results of this study were the following: (*a*) vaccination done shortly before or even after the onset of the epidemic was found to exert a protective effect with a total attack rate of 2.22 per cent among the 6263 vaccinated and 7.11 per cent among the 6211 controls, a ratio of 1 to 3.2, or in other words, the number of infections was reduced more than two thirds; (*b*) the influence of the vaccine was most clearly evidenced at the height of the epidemic prevalence; (*c*) the effect of the vaccine became evident in about one week after inoculation but the duration of the effect was not ascertained. As a result of these studies, the War Department announced (J.A.M.A., September 30, 1944) that should influenza occur in epidemic form in the Army all personnel under risk of exposure to the disease would be vaccinated.

Local Use of Antiserum.—After the preliminary animal experimentation of numerous workers in several parts of the world, Smorodintsev, in 1940, reported successful immunization in man by the intranasal spraying of serum of highly immunized horses. During an extensive epidemic in Leningrad, 501 volunteers were given the intranasal medication in two doses at fifteen day intervals, 1825 untreated individuals being used as controls; the incidence of

infection in the treated cases was 0.4 per cent and in the untreated 8.2 per cent. It would therefore seem that in the event of an epidemic we may expect some protection from this type of passive immunization. Powell (1944) developed a rabbit antiserum and suggested that after initial influenza cases have appeared in a community about 1 cc. of this antiserum be used per person as follows: 0.3 cc. to be sprayed into each nostril, and 0.3 cc. sprayed over the fauces (it is said that the average bulb atomizer delivers about 0.1 cc. at one discharge). In case an atomizer is not available a medicine dropper can be used but is not as satisfactory in securing proper distribution of serum. Powell suggested that the antiserum should be used once weekly throughout the duration of the epidemic.

Antiseptic Gargles and Sprays.—During the 1918 pandemic the earth trembled and fizzed from the gargling and spraying of the more enlightened portions of its populace in all the hemispheres, but it is not a matter of record that any cases of influenza were thereby prevented. However, MacNeal and Parker (1944) cited some *in vitro* experiments in which they found the virus of influenza inactivated by such mild germicidal agents as the Liquor Antiseptic N.F. VII—and so I suppose that in the next pandemic, which many observers feel to be almost certainly imminent, these agents will be much employed again; certainly no one can deny that a good resounding gargle is a tremendous morale booster.

The Face Mask.—The ordinary gauze mask was much used by hospital personnel during the 1918 pandemic, but recent studies have shown that it is probably not only useless but actually harmful. However, there has been developed a new type of mask containing flannel filters which is said to provide protection to the wearer and to the exposed susceptible and to become more efficient with use and laundering; Francis (1943) said that in his opinion the new mask deserves a place in the field of prevention.

Aerosols and Ultraviolet Irradiation.—These matters are discussed under Common Cold.

LEISHMANIAL INFECTIONS

(Kala-Azar or Visceral Leishmaniasis, Oriental Sore or Cutaneous Leishmaniasis, American or Mucocutaneous Leishmaniasis)

Kala-azar (*dumdum fever*) is common in certain parts of India, in China, Indo-China, the Middle East and Arabia, all around the shores of the Mediterranean (where it occurs principally in young children in the spring and summer), in southern Russia, and in North, Central, East and West Africa. Until very recently it has been considered not to occur in the western hemisphere except for an occasional imported case, but the studies of Penna (1934) in Brazil disclosed a number of infections there and we now know that even earlier reports had revealed the patchy existence of the disease in several countries of South America. Kala-azar is caused by *Leishmania donovani*, a protozoan organism, and everywhere that the disease is encountered in man it occurs in dogs also, with the possible exception of India. The study of Swaminath, Shortt and Anderson (1942) completed the evidence which incriminated sandflies of the genus *Phlebotomus* as the vector between man and man. But there are many sandflies and apparently many strains of *L. donovani;* it

seems that for each locality there must be the right species of *Phlebotomus* and the right strain of the parasite. And the possibility that infection may rarely occur without the intervention of the fly has not been entirely discarded, for in rare instances viable organisms have been found in the urine, and Forkner and Zia's (1935) finding of viable organisms in the nasal and oral secretions of patients in China has apparently been confirmed by workers in India. The organisms, however they may enter the body, embed themselves in the endothelial cells lining blood and lymph vessels particularly in the spleen, liver and bone marrow, whence they burst into the blood or lymph stream to be engulfed by other endothelial cells or by leukocytes.

The onset is often insidious, though it may be acute. Usually the first complaint is of several bouts of fever with increasing weakness. In one fourth to one third of the cases the fever is of the double-remittent type, *i.e.*, with a rise and fall twice or thrice in the twenty-four hours; in the majority of cases it is of a very irregular sort. Emaciation and, later, anemia (proportionate reduction in red cells and hemoglobin) are pronounced and there is a striking leukopenia with a pronounced reduction in polymorphonuclears and increase in mononuclears and lymphocytes. Sometimes the body assumes a dusky hue (*kala-azar:* "black sickness"), the cause of which is not definitely known. Great enlargement of the spleen, and frequently later enlargement of the liver, cause the abdomen to be markedly protuberant, but the absence of splenomegaly or hepatomegaly in an early case does not exclude the diagnosis. In China and Brazil painless adenopathy of the neck has been recorded; Cole (1944) observed enlargement of one or another group of glands, the inguinal and femoral most frequently, in half of his cases in East Africa. Daily rigors are common, though other pronounced symptoms are rare. Manson-Bahr (1940) said that outstanding features of the disease are the absence of malaise and the maintenance of good appetite; Cole (1944) remarked these things in the beginning in the majority of his cases also. Diarrhea may be due to the leishmanial infection or to concomitant bacillary, amebic, or flagellate dysentery; both Cole (1944) and Burke (1944) remarked abdominal pain as a not infrequent early symptom. The febrile periods are followed after two to six weeks by afebrile periods, and then further attacks of fever. Obtaining the organisms by hepatic or splenic puncture is sometimes necessary in order to make the diagnosis, but sternal puncture bids fair to replace these dangerous procedures. When present in the peripheral blood the leishmania are to be found in leukocytes; they may be cultured *in vitro* and established in experimental animals, the Chinese hamster being best suited for the latter purpose. Cole (1944) established quite definitely an incubation period of two to four months for the cases which he studied in East Africa. In India and Africa and apparently to a lesser extent elsewhere there have been observed rashes which come on when the patient is beginning to recover from visceral leishmaniasis under the influence of drugs or perhaps some time after the recovery has been completed; leishmania may be found in smears from these skin lesions.

Kala-azar has decimated whole populations in its time. It is said that Indian villagers have burned alive many of its victims, after first stuporizing them with alcohol, in the attempt to stamp out the disease. About 90 per cent of the untreated cases succumb in two months to two years, the immediate cause of death usually being a secondary infection. Cancrum oris, said formerly to occur in about 17 per cent of cases, is nowadays not so frequently seen since a satisfactory form of treatment has been developed; not only the mouth may

be involved, for the gangrene may affect such other sites as the cervix of the uterus, the bowel, the lung and the external genitalia. Zia and Forkner (1934) called attention to the occurrence of acute agranulocytosis as a complication of kala-azar in China and speculated upon the possible connection of this with the appearance of cancrum oris; according to Das Gupta (1943) agranulocytosis occurs with extreme rarity in the cases in India.

Oriental sore (*Delhi boil*) is a cutaneous leishmanial infection which occurs both endemically and epidemically in many tropical and subtropical regions in both hemispheres. The disease is caused by *L. tropica* and has recently been shown by Russian workers, whose contributions have been thoroughly and critically reviewed by Hoare (1944), to be conveyed by the bite of the sandfly as in the case of kala-azar and to reside in burrowing rodents as reservoir hosts. However, the possibility of direct transmission from person to person still exists since the organisms are recoverable from the lesions; one such case, possibly contracted in this manner in the United States, was reported by Gelber (1942). The lesions, which are usually multiple, are found on exposed parts of the body, chiefly the face, ears, limbs and on the exposed areas of the trunk; Avery (1942) said that there has been no recorded case of a lesion on the scalp, palms or soles. All races and ages and both sexes are affected, but in endemic areas most of the cases are seen in children. The existence of different clinical forms of oriental sore has been recognized all over the world for a long time, but the Russians effected a distinct separation of two clinical forms: the "dry" type which is prevalent in towns and in which the papules persist for months before they ulcerate, the course of the disease being chronic; and the "moist" type, which occurs in the open country and in which the lesions ulcerate in about a week or two and the process tends to run an acute course. It is said that in the moist type the incubation period is one to six weeks whereas in the dry type it may be from two months to a year, that in the moist type lymphangitis occurs commonly while it is rare in the dry type, that few parasites are present in the lesions of the moist type but that they are numerous in those of the dry type, that the moist type occurs principally in the summer and fall while the dry type occurs perennially, and finally that it is only in the moist type that the rodent reservoir host has been definitely identified. A diagnostic skin test, which is said to be highly specific, has been developed by the Russians.

American or mucocutaneous leishmaniasis, from the lesions of which *L. braziliensis* is recovered, is prevalent in southern Mexico, Central America and tropical South America (where it is known also as "espundia" and "uta hemeda"). Shattuck (1938) pointed out that sandflies of the genus *Phlebotomus* have been found in all regions of the Americas where leishmaniasis exists with the exception of Peru, for which data were lacking; Pesce and Pardo (1943) more recently supplied evidence that this sandfly occurs in the latter country also. In these mucocutaneous cases the ulcerations involve the ears, nose, mouth and pharynx in very extensive areas of necrosis, the patient often becoming very cachectic and severely disfigured. While ulcerating lesions of the mucosae are occasionally seen in epidemic regions elsewhere in the world, Strong (1942) stated that he had not observed lesions just like those in the American cases anywhere else in the tropics. These mucocutaneous cases, however, comprise only a small proportion of the total number of cases of cutaneous leishmaniasis seen in the Americas.

THERAPY

Pentavalent Antimony Compounds.—Antimony sodium tartrate or antimony potassium tartrate, better known as "tartar emetic," is the classical specific drug in the leishmaniases, but its high toxicity, the fact that it can only be given intravenously, that the time required for the administration of a complete course is very long, and that many cases are completely resistant to it from the very start—these things have made it far from an ideal drug with which to attempt the eradication of a disease affecting large numbers of people. In the search for a better drug certain pentavalent antimony compounds that are salts of para-aminophenylstibinic acid, or substitution products of the same, have been produced. These compounds are certainly much less toxic than tartar emetic; they can be given in larger doses, thus reducing the average time required for treatment from two or three months to about three weeks (or to eight or ten days in the case of neostibosan, which can be administered daily); and they are suitable for either intramuscular or intravenous injection. Also, they are apparently much more effective than the earlier drug, there being fewer relapses among those treated with the pentavalent compounds and a considerably lower death rate—4.2 per cent in Napier's series of 167 cases of kala-azar treated with six different pentavalent compounds as compared with 14.4 per cent in his series of 139 tartar-emetic-treated cases. Unfortunately, the new drugs are much more expensive than the tartrates and the cutaneous forms of leishmaniasis do not seem to respond to them much better than they did to the older drugs. It should be noted, furthermore, that the Indian cases and perhaps those in China as well have always responded much better to these drugs than have the cases in the Sudan, the Mediterranean area and élsewhere.

Neostibosan.—Napier and Mullock (1929), in India, gave a daily intramuscular injection of 0.3 Gm. for eight days, the total dose therefore being 2.4 Gm. Sati (1942) in the Sudan used such dosage intravenously daily or on alternate days for a course of 15 injections. Struthers (1931), in Tsinan, felt that the Chinese patient will not tolerate quite such high individual doses. In his series of 87 cases, the initial adult dose was 0.1 Gm. intravenously and subsequent doses of 0.2 to 0.3 Gm., sometimes daily and sometimes every other day; the average total dose was 2.63 Gm. and the average time under treatment was 23.3 days. In children, both intravenous and intramuscular injections were given, the initial dose of 0.05 Gm. being followed on alternate days by 0.2 Gm.; average total dose, 2.1 Gm., and the average time under treatment, thirty-two days. Lee and Chu (1935), at the Peiping Union Medical College, found an adequate course for a child was 1.5 to 2.5 Gm.; for an adult, 4 to 5 Gm. Manson-Bahr's (1940) total dosage to effect a cure has been 2.7 to 4.0 Gm.

Solustibosan.—One apparent advantage of this drug is that it is available in the form of a stable solution ready for injection. It is used intramuscularly and also intravenously and apparently toxicity is lower than that of the other compounds. Struthers (1937) and Yates (1937) reported good success with it in China, Napier (1937) in India, Sati (1942) in the Sudan. The last gave it in courses of 8 injections given daily or on alternate days as follows: first day 2 cc., second day 4 cc., third day 6 cc., fourth day 8 cc., fifth, sixth, seventh and eighth days 10 cc., making a total dosage of 60 cc. for a single course.

Concentrated Solustibosan.—Kikuth and Schmidt (1943) reported the preparation of a solustibosan suspension administered intramuscularly to be ab-

sorbed from an oil depot. It was said that in children treated with this new preparation in Spain, both local and general tolerance was good when the drug was used in a dose of 1 cc. per kilogram body weight, the full course consisting of 5 injections at two-day intervals. Remarkably fine results were said to have been achieved. In these Spanish cases a concentrated solustibosan solution five times the original strength was also employed, and it was said that satisfactory results were obtained by administering the drug every twelve hours, a total quantity of 0.4 cc. per kilogram of body weight being given in 10 injections in five days. I have seen no record of trial of these newer preparations in adults.

Urea Stibamine.—This drug has been much used in Asia. Rogers said that principally by its use the Assam Government cleared up over 300,000 cases between 1923 and 1935. Cole (1944), in East Africa, found this the most valuable of the drugs that he tried. What he called his slow dosage corresponded roughly with the standard dosage of Brahmachari who introduced the drug: injections every two to three days, starting with 0.05 Gm. and gradually rising; total 2.0 to 2.5 Gm. in 15 to 25 injections in twenty to fifty days. His more intensive course consisted in giving the patient 14 daily injections of 0.05, 0.1, 0.15, 0.2, etc.; total 2.5 Gm.

Neostam.—The recommended intravenous dosage of this agent in Circular Letter No. 33. Surgeon General's Office (1943), was 15 doses on alternate days, the first dose of 0.2 Gm. and subsequent doses of 0.3 Gm., a total dose of 4.4 Gm. In cases of cutaneous leishmaniasis, Ball and Ryan (1944) used smaller dosage giving injections twice weekly, the first of 0.05 Gm., the next 0.1 Gm., the third 0.15 Gm., and the fourth and all succeeding ones 0.2 Gm.; in a few individuals who had frequent untoward reactions the maximum dosage was kept at 0.15 Gm. The average individual received 1.14 Gm. of neostam. Of Ball and Ryan's 221 cases of oriental sore thus treated, 207 were said to have been cured.

Stibosan (*von Heyden* 471).—In Napier's series (1926) of 104 cases, the average total dosage was 2.78 Gm., the average number of injections (three times weekly) was 13.3 and the maximum dose was 0.3 Gm. Manson-Bahr (1940) said the initial dose is 0.1 Gm. but may be 0.2 Gm. for robust individuals, though it should be reduced to 0.05 Gm. for weak patients. He said children tolerate the drug well; for a three-year-old beginning dosage is 0.025 Gm., increasing to 0.05, 0.075, 0.1 Gm., and from twelve years up 0.25 may be reached. The drug may be given either intravenously or intramuscularly.

Neostebene.—In 1941 Brahmachari, who introduced urea stibamine, brought forward this new drug which was given in a dose of 0.1 Gm. twice a week in a series of 10 cases until a total of 1 to 4 Gm. had been given. The treatment was apparently highly successful but I have seen no further reports.

Stibatin.—This new agent has been the subject of a preliminary report by Burke and Chakravarty (1944) in India, who used it in a small series of cases of kala-azar and felt it to be as good as, if not superior to, other antimonial agents. The drug is given according to one of the following three schemes: (*a*) slow treatment with increasing dosage—2 cc. on the first day, 4 cc. on the third day, and 9 subsequent doses of 6 cc. each on alternate days; (*b*) accelerated treatment—2 cc. on the first day, 4 cc. on the third, 6 cc. on the fifth, 8 cc. on the seventh day, and 4 subsequent doses of 10 cc. each on alternate days; (*c*) continuous treatment—6 cc. daily for ten days. Stibatin is said to be relatively nontoxic, not to cause after-pain with intramuscular use, and to be inexpensive compared with its rival antimony products.

Reactions.—The chief reactions when antimony is employed are the following: dizziness, coughing, vomiting, diarrhea, muscle and joint pains, hepatitis (necessitating immediate cessation of the treatment), severe headaches and rigors, pronounced slowing of the heart and frightening cessation of the respirations. When using tartar emetic itself, it is said that a somewhat rare drug-induced complication is acute arthritis which usually beneficently influences the course of the primary disease. With the pentavalent antimonials none of these reactions are upon the whole so severe as those seen during the use of tartar emetic, nor do they occur with anything like as great frequency.

Tartar Emetic.—If the expense of a course of treatment with one of the above drugs were to be very markedly reduced there would likely be no point

TABLE 4.—TARTAR EMETIC DOSAGE IN KALA-AZAR

Time.	Adults.		Children 10 to 15 years.		Children under 10 years.	
	Cc. of 2 per cent sol.	Gm. of drug.*	Cc. of 2 per cent sol.	Gm. of drug.*	Cc. of 2 per cent sol.	Gm. of drug.*
First week 1st injection	1.5	0.03	1.0	0.02	0.5	0.01
2nd injection	2.0	0.04	1.0	0.02	0.5	0.01
3rd injection	2.5	0.05	1.5	0.03	1.0	0.02
Second week 1st injection	3.0	0.06	1.5	0.03	1.0	0.02
2nd injection	3.0	0.06	2.0	0.04	1.5	0.03
3rd injection	3.0	0.06	2.0	0.04	1.5	0.03
Third week 3 injections of	3.5	0.07	2.5	0.05	2.0	0.04
Fourth week 3 injections of	4.0	0.08	3.0	0.06	2.5	0.05
Fifth week 3 injections of	4.5	0.09	3.0	0.06	2.5	0.05
Sixth week 3 injections of	4.5	0.09	3.5	0.07	2.8	0.056
Seventh week 3 injections of	5.0	0.10	3.5	0.07	2.8	0.056
Eighth week 3 injections of	5.0	0.10	3.8	0.076	3.0	0.06
Ninth week 3 injections of	5.5	0.11	3.8	0.076	3.0	0.06
Tenth week 3 injections of	5.5	0.11	3.8	0.076	3.0	0.06
Eleventh week 3 injections of	6.0	0.12	4.0	0.08	3.3	0.066
Twelfth week 3 injections of	6.0	0.12	4.0	0.08	3.3	0.066
Total	...	3.27	...	2.27	...	1.81

* This column is added by me.—H. B.

in retaining a description of methods employed with the classical drug, but since events in the world today seem to be tending to promote just the opposite effect, I shall still give a brief outline of the use of tartar emetic. As in the last edition of this book it seems to me that the dosage scheme is best presented in a modification of Young's table (Table 4). This drug must be given intravenously since its intramuscular injection is very painful and almost invariably causes necrosis. The solution is sterilized before administration. In infants, in whom intravenous therapy is sometimes impossible, administration of tartar emetic is often quite difficult. Saha (1931) reported the successful treatment of 5 cases with rectal injections, introducing 2 cc. of a 0.25 per cent solution after cleansing the rectum with normal saline. The dose was increased 2 cc. in an injection given every second day until 8 cc. had been given; then in-

creasing 1 cc. in an injection every fourth day to 12 cc. in children up to three years; in a girl of ten years he went up to 24 cc. Rectal irritation was not caused. Most authorities consider that both oral and rectal administration usually fail because antimony is absorbed in insufficient quantities, which may cause the infecting organisms to become antimony-resistant or "fast"; however, Chavarria *et al.* (1944) stated that they had used the drug successfully by mouth in a number of cutaneous cases, employing a solution containing 2.5 Gm. of the drug in 100 cc. of chloroform water, one drop of this solution containing approximately 1 mg. of tartar emetic. In children treatment was commenced with one drop daily and was increased by a drop every three or four days until the limit of tolerance without diarrhea or vomiting was reached; in adults the initial dose was 5 to 15 drops. Intraperitoneal injection in very dilute solution in physiologic saline was used successfully by Smyly in the cure of a case of kala-azar in an infant, aged six months; however, Caronia (1930), whose experience in the disease was vast, pointed out the at least potential danger of setting up a severe peritoneal inflammation.

Stilbamidine.—Of the three diamidine compounds introduced in recent years, propamidine, pentamidine and stilbamidine, the latter, which is diamidine stilbene and does not contain antimony, seems to have been found the most potent in the treatment of the leishmaniases. It seems that not only the relatively easily treated cases of kala-azar in India but also the more resistant Mediterranean and Sudan forms of the disease have responded well to this drug. In India, Napier *et al.* (1942) treated 100 cases of kala-azar with this agent, the patients being in all stages of the disease. The drug was administered intravenously in a 1 per cent solution in distilled water in 95 of the cases and in the remaining 5 cases intramuscularly, but the latter proved to be very painful. In over 90 of the cases, in which no previous treatment had been given, 10 or 12 daily doses were given; in the others, which were resistant cases, up to 15 injections were given. The dosage finally adopted for adults was an initial dose of 0.025 Gm. followed by doses of 0.05, 0.06 to 0 075 according to reaction, 0.09 and 0.1 up to a maximum of 1 mg. (0.001 Gm.) per pound of body weight. In small children the initial dose was 0.01 Gm. up to a slightly higher dose than 1 mg. per pound of body weight, as children tolerated the drug better than adults. After the injection of the agent the blood pressure nearly always showed a marked drop and sometimes the reaction was very alarming to both patient and physician, though it was found that it could be controlled by giving an injection of 0.25 cc. of 1:1000 epinephrine solution just before administration of the drug. Kirk and Henry (1944) felt that these immediate reactions precluded the use of the intravenous route for outpatients. Ninety-eight of the patients in Napier's series were cured and 2 died; of the 98 cured cases 2 relapsed and of these 1 received a second course of the drug. In 17 of these cases there also developed a delayed neurological syndrome the principal features of which were paresthesia and partial anesthesia in the trigeminal area with a loss of sensation of light touch, with preservation of sensation of pain, temperature and pressure. Sen Gupta (1943) of Napier's group said that this condition is not dangerous to life and is not progressive and that in most patients there occurred a tendency to slow recovery. This latter author felt that in view of both the immediate and the delayed reaction, and especially since equally good results can be accomplished with the pentavalent antimonials, stilbamidine is not likely to become the preferred drug, at least in India, except in antimony-resistant cases. An

early type of fatal reaction which gave some trouble with stilbamidine in the beginning was shown by Fulton and Yorke (1942) to result from the use of stale solutions; since the drug is employed at once upon making the solution these severe reactions are no longer seen.

Local Therapy in Cutaneous Leishmaniasis.—In a review of locally employed agents, Avery (1942) included the following: (*a*) Berberine sulfate injected by means of a tuberculin syringe in 2 per cent solution into the indurated area surrounding the ulcer, about six weekly injections being required for each ulcer in order to infiltrate the whole circumference, 1 cc. of solution usually sufficing; no further injections are to be made until any inflammatory reaction which occurs has subsided. Three to six injections have been found sufficient to effect a cure but the treatment is not recommended when there are more than six ulcers. (*b*) The local application of a 4 per cent tartar emetic ointment or of dressings with tannic acid powder or magnesium sulfate paste after scraping of the lesion. (*c*) The sulfonamides locally applied have some claimed cures to their credit, as has also cignolin (anthralin, closely related to chrysarobin) in ointment form. (*d*) Injection of a 2 to 5 per cent solution of emetine into the thickened edges and bases of the ulcers, using not more than 20 minims at a time. (*e*) The Dickson-Wright method of covering the wound directly with adhesive strapping and leaving it without further dressing for a week or more after thorough scraping and treating with liquefied phenol under an anesthetic. Local measures not covered by Avery are the following: atabrine, which Dobrotvorskaya (1941) described as being used in 5 per cent solution injected at several points into the dry type of lesion, both the injections and the 3 per cent solution being employed in treatment of wet lesions; Ball and Ryan (1944) used local injections of 2 per cent neostam solution with good results in 32 of 35 cases; the authors just referred to tried ethyl chloride spray but with very poor results, though freezing with carbon dioxide snow has been reported to be a very satisfactory form of treatment in India; there have been a number of reports of the successful use of roentgen therapy; Bobrov (1942) advocated the withdrawal of 5 to 10 cc. of blood which is soaked up into a cloth and applied to the sore, this being repeated at one to four or five-day intervals, the results being reported as very good, but it should be noted that the cases were of the moist type which ordinarily have a comparatively short duration; Gupta and Kahali (1944) reported the successful employment in a small series of cases of umbellatine, an alkaloid resembling berberine, in much the same way in which berberine is applied locally. Dubovsky (1942) reported the successful employment of a vaccine made from killed cultures.

PROPHYLAXIS

Sokolova, whose work was critically reviewed by Hoare in 1944, described the results of large-scale vaccinations against cutaneous leishmaniasis in Middle Asia, using material from both the dry and moist types of lesion, the inoculations being made directly from human lesions or with living cultures. The incubation period varied from a fortnight to a year (average four to five months) while the infection lasted from two to seventeen months (average six to nine months). The total number of persons vaccinated was 1522 of whom 1107 were followed up; the vaccination was successful in 73.8 per cent, best results being obtained with cultures of parasites from sores of the moist variety. The effectiveness of this type of "vaccination" in protecting against

new infection is shown in the following figures: among 772 successfully vaccinated persons only 6.3 per cent subsequently contracted the natural disease while in unsuccessfully vaccinated persons natural infections were acquired by 29.3 per cent, these figures to be compared with the incidence of 63.6 per cent in the nonvaccinated population. It became apparent in these studies that the development of immunity as the result of vaccination is a slow and gradual process requiring about a year, thus explaining the susceptibility to superinfection in a certain proportion of the vaccinated persons. Successful vaccination upon a somewhat smaller scale has also been reported by Katzenellenbogen (1944) in Palestine.

LEPROSY

There are five major infectious diseases whose entire handling has been taken over quite properly by public health authorities or other specialists of great experience. These five are Asiatic cholera, leprosy, plague, trypanosomiasis, and yellow fever; and since they do not nowadays raise problems in treatment for the general practitioner, I shall no longer allot space to a consideration of them in this book.

LEPTOSPIROSIS

(*Weil's Disease, Spirochetal Jaundice*)

This is an acute infectious disease caused by *Leptospira icterohaemorrhagiae.* Onset is usually abrupt with vomiting, headache, fever, muscular pains, especially in the calves of the legs and the abdominal wall, and great prostration; sometimes there is initial chill or chilliness, transient stiffness of the neck, labial herpes, hiccup and cough; conjunctival injection is often present. There is leukocytosis of high degree, and nosebleed, purpura, petechial and subconjunctival hemorrhages, bleeding mucous membranes, hematemesis and melena evidence a probable local toxic effect of the spirochete on the capillary walls. The urine early contains bile and may show all the evidences of acute toxic nephritic or nephrotic changes. In about half the cases the temperature falls in three or four days to a week and the patient goes on to recovery, but in the other cases jaundice appears at about the time the temperature falls and the liver becomes tender and swollen; the spleen may be palpable. In these severely ill patients there is an increase in the hemorrhagic tendency and often renal failure occurs; delirium or semi-coma and a rash often appear, but the temperature usually remains low. Bruno *et al.* (1943) said that symptoms and findings referable to the heart were not uncommon in their experience, and a similar observation was made by Senekjie (1944). On the Continent and in England (Lescher, 1944), a meningeal form of the disease is recognized and the statement of Ashe *et al.* (1941) that it occurs in our country also was corroborated by the findings of Clapper and Myers (1943) and Senekjie (1944). Strong (1942) stated that in Japan the mortality rate is as high as 48 per cent while in Europe it ranges from 4 to 32 per cent; in Senekjie's (1944) 30 cases in the United States the mortality rate was 16.3 per cent. In those surviving

the severe attack defervescence usually begins at the end of the second week, but there are sometimes one or more mild relapses and convalescence is often very protracted. Leptospiral vegetative endocarditis, iridocyclitis (and much more rarely optic neuritis) have been recorded as late complications.

The causative organism is present in the blood up to the seventh day and appears thereafter in the urine where it persists for a long time after recovery. It seems that darkfield examinations for *L. icterohaemorrhagiae* are very misleading. The blood also gives a positive agglutination reaction; Ashe *et al.* said that if this reaction is negative after thirty days Weil's disease may be ruled out, a statement which certainly does not indicate that much diagnostic aid is to be expected from this test early in the attack. The diagnosis was made by the agglutination reaction in 80 per cent of Senekjie's cases, the titer beginning to rise during the hepatic stage, reaching the diagnostic level during the nephritic stage and being at its peak during convalescence; in Senekjie's opinion the titer must be at least 1:300 with a steady rise in order to be of diagnostic significance, but Tiffany and Martorana (1942) believed that a titer of 1:1000 is indicative of present or recent infection. The newest laboratory contribution consists in injecting blood and urinary sediment from the patient into a young guinea pig which will become febrile in a few days and is said to yield the organism from its aspirated peritoneal fluid before death; in connection with this test, Murgatroyd (1943) suggested that alkalis be given the patient in order to render the urine alkaline before taking a specimen since the organisms soon die in acid urine. The same organism is found in wild rats the world over, and it is significant that most recorded sporadic or epidemic cases have occurred in individuals who have passed some time in wet, rat-infested places, such as military trenches and civilian excavations, natural swimming pools, mines, sewers, dirty canals, rice-paddies, dank fish-handling establishments and slaughterhouses, or have drunk water from such places. One American outbreak was presumably traced to infected holy water in use during a religious novitiate. Insects have been shown not to be intermediary hosts, the water or slime being infected directly from the urine of the rat; *L. icterohaemorrhagiae* will live in stagnant water for three weeks. The organism has often been found in the urine of dogs, cats, foxes, field mice, pigs and horses; laboratory workers have become infected from albino rats that had been infected by wild rodents; guinea pigs are occasionally, but white mice more often, carriers of the disease. The organism has been passed from dogs to man in a number of instances, but passage from dog to dog has not been proved, which indicates that the dog likely obtains it from the carcass of one of the other carrier animals; but there is a serious infectious jaundice in dogs (dog typhus or Stuttgart disease), which is caused by *L. canicola;* man has been infected by contact with these dogs, but this canine organism does not occur in rats. Man-to-man infection with *L. icterohaemorrhagiae* is apparently very rare though a case has been reported of transmission by copulation and it seems that intrauterine infection of the fetus can occur.

Weil's disease occurs all over the world and in some areas the incidence is rather high; that we will find many more cases than hitherto suspected in the United States was indicated by the fact that 30 cases were diagnosed in the Charity Hospital of New Orleans from September, 1939, to February, 1944 (Senekjie). Males preponderate among the patients and children are rarely affected; most cases occur during the summer. In an epidemic among laborers in the Andamans, the onset of the first case was six days after the beginning

of work in a leptospira-infested swamp; Schüffner (1934) found an average incubation period of 10.3 days in 452 cases in Holland.

Weil first described this disease in 1886, and Inada and Ido discovered the causative organism in 1914.

THERAPY

One would be hopeful of the intravenous arsenicals here, but they have failed; indeed, some cases have been made worse by their use, probably because of the state of the liver. The antimonial drugs have also failed. Studies with experimental animals have indicated that bismuth might have real value, but years have passed and there has still been no thorough trial in the human. The sulfonamides have been tried without success; Heilman and Herrell (1944) proved the therapeutic effectiveness of penicillin in experimental infections in guinea pigs but I have seen no record as yet of the trial of this agent in the human. An apparently potent antiserum prepared by raising the agglutinating titer of horse serum was originated in Japan and is successfully and widely used there and in Europe, but it is still not available in the United States. In Hawaii the serum has been obtained from Japan and used satisfactorily by Tokuyama (1940). Davidson and Smith (1939), in Scotland, said that 10 to 20 cc. are given intramuscularly or intravenously and the dose repeated in four to six hours, but Tokuyama strictly followed Inada and Ido's instructions to give 40 cc. intravenously every twenty-four hours. Also in Hawaii, Keay (1938) successfully employed transfusions from a convalescent donor and obtained "spectacular" results in his two cases. Ashe *et al.* (1941) also transfused convalescent blood in a single case—the patient had been anuric for thirty hours but began to void six hours after the transfusion; antibodies, previously absent, appeared in, and leptospira disappeared from, the blood. However, 250 cc. of convalescent whole blood were given in the fourth week of the disease to one of Senekjie's patients without appreciable results.

Since in most cases the treatment must obviously be symptomatic, Senekjie (1944) advised that the patient be given high carbohydrate, high protein and high vitamin diets to support the liver and that calcium gluconate be administered parenterally. Fluids must be pushed; for the treatment of anuria see Index.

PROPHYLAXIS

In Japan, large-scale employment of horse antiserum has been made in prophylaxis, but Walch-Sorgdrager (1939) said that this is not routinely done in Holland even in the case of an individual who has fallen into one of the highly infected canals; only 1 in 75 such persons contracts the disease and to such a one the serum is administered upon the first appearance of symptoms. However, Schüffner (1941) used prophylactic injections in 21 individuals who had been exposed through handling a colony of infected rats; but he employed a vaccine made from rich cultures of the organism, subjected twice for thirty minutes to 70° C. and injected intravenously, first 1 cc. and on the eighth day 2.5 to 3 cc. (a few reactions of an allergic nature he felt could have been avoided if the second injections had been given on the sixth day).

The dejecta, being infectious, had better be disinfected and disposed of, and the attendant's hands as well cared for as in typhoid fever. Cotter and Sawers (1934) concluded that carriers are probably not important in spreading the disease; there would likely be no point in keeping the patient in hospital until the urine is free from organisms.

MALARIA

This day relenting God
Hath placed within my hand
A wondrous thing; and God
Be praised. At His Command

Seeking His secret deeds
With tears and toiling breath
I find thy cunning seeds,
O million-murdering Death.

I know this little thing
A myriad men will save.
O Death, where is thy sting
Thy victory, O Grave!

Before Thy feet I fall,
Lord, who made high my fate;
For in the mighty small
Is shown the mighty great.

—Lines written by Ronald Ross on finding himself in possession, after infinite toil, of conclusive proof of the causal relation of the mosquito to malaria.

Malaria is an infectious disease caused by plasmodia conveyed from infected to healthy persons by the bite of the females of certain mosquitoes of the subfamily *Anophelinae*, in whose body the organism passes a part of its life cycle. When the mosquito bites a malaria-infected individual she takes into her stomach two forms of plasmodium, schizonts and gametocytes, the latter being called "crescents" in the case of falciparum infection. The schizonts are destroyed just as any other food substance, but the gametocytes, which are sexual forms, survive and fertilize and eventually give rise to active sporozoites, which make their way into the salivary glands and are then injected into the blood of an individual subsequently bitten by the mosquito. In certain of the bird malarias it has been found that these injected sporozoites enter and inhabit the lymphoid-macrophage system and endothelial cells and occasionally heterophiles and eosinophiles, and that entrance into the erythrocytes is only made by forms thereafter erupting from these tissue cells. Such an exoerythrocytic stage has not yet been unequivocally demonstrated in man, and therefore at present we can only say that after a time, having undergone a metamorphosis somewhere, the sporozoites injected by the mosquito reappear as plasmodia in the red blood cells, where they mature and finally erupt into the blood stream as a shower of schizonts (asexual forms) and gametocytes (sexual forms). The gametocytes cause no symptoms and finally die if not taken out of the blood again by a mosquito, but the schizonts reenter fresh red blood corpuscles and repeat the cycle, giving rise to the symptoms of the disease. The accepted species of human plasmodia are *Plasmodium vivax*, *P. malariae*, *P. falciparum* and *P. ovale*. The last-named species is thought of as occurring principally in West and Central Africa, and since these are the regions inhabited by the great apes it has been looked upon by some observers as a form of monkey malaria just becoming adapted to man; however, it has recently been reported from China, Colombia and the Philippines and possibly in the course of time it will be differentiated elsewhere. Ovale infection is extremely mild and will not be the subject of special description in this book. *P. perniciosum*, *P. tenue*, and *P. aethiopicum*, each of which was at one time proposed as a special species, are all now generally accepted as local variants of *P. falciparum*. Wenyon (1941) and Coatney and Young (1941) agree that full proof of the specificity of *P. wilsoni* is yet to be demonstrated.

In a recent authoritative review, Boyd (1944) made the important point that clinically active malaria infections regardless of the species of their causative parasites exhibit three basic symptoms: (*a*) fever, (*b*) anemia and (*c*) splenomegaly. In vivax or benign tertian malaria (*P. vivax*), the patient may feel vaguely apathetic and experience some headache and muscle and joint

pain for a few days before the end of the incubation period, but the first objective finding is that of fever, which will either precede or follow by several days the appearance of the organisms in the blood. The temperature may rise as high as 107° F. (41.6° C.) or more and in a primary attack will continue for some days to be remittent or irregularly intermittent. During this period the patient feels extremely ill and suffers from severe head and muscle and joint pains. The transition from remittent to intermittent is usually gradual so that it is often ten days or more after the onset of a primary attack before the patient experiences his first true paroxysm of chill, fever and sweat and the intermittent character of the paroxysms becomes apparent. This rigor is in a few instances little more than a slight sensation of chilliness but usually it consists in a sensation of very intense cold accompanied by violent involuntary muscular contraction. During the chill the temperature is rising but the peak of the chill is passed before the temperature has reached its peak. In these paroxysms the temperature remains elevated for six to twelve hours, then profuse perspiration sets in and the temperature falls rapidly by crisis. If untreated, the patient may continue to have recurrent paroxysms for as long as three months with occasional spontaneous remissions. Some patients experience nausea and vomiting with each paroxysm and sometimes urticaria accompanies the paroxysms also. After the disease has become well established extensive herpes labialis frequently appears, occasionally dependent edema, and sometimes jaundice if the destruction of erythrocytes has been very rapid. Anemia in vivax malaria, though often severe enough, is not so rapidly progressive as that seen in falciparum infections. Splenic enlargement is usually detectable during the second week of the primary attack, the organ being tense and tender; during this first attack the spleen may reach the level of the umbilicus and may or may not completely recede during the succeeding period of clinical inactivity. A small amount of albumin in the urine is a very variable finding in vivax infections. A case of vivax malaria running such a course as that above sketched is very rarely seen in the more fortunate parts of the world whose inhabitants can afford the purchase of antimalarial drugs which quickly terminate the attack. However, even though the primary attack is promptly arrested by proper treatment, the occurrence of one or more relapses is to be expected in a discouragingly large number of patients. These relapses occur most often during the first year; the most severe one may usually be expected between the seventh and tenth months following the initial attack, and the last of them is usually experienced before the end of the second year—but Manson-Bahr (1934) said that they may be expected for as long as four years, and Boyd (1944) admitted the possibility up to three years. Apparently the relapse rate following each attack is lower than that for its predecessor; witness the fact that Dieuaide (1945) said that while a second attack is experienced by 70 to 80 per cent of persons infected, by the time one gets to the tenth or fifteenth attack the fraction of the original group is very small, perhaps 1 in 1000 or less. It is during the relapses that the tertian character of the paroxysms is most characteristically manifested. Though vivax malaria may induce miscarriage or premature labor or death of the fetus *in utero* the prognosis with regard to the life of the patient himself or herself is extremely good. Death from a ruptured spleen or from acute anemia has been recorded in rare instances, but in most cases in which a patient with vivax malaria has come to autopsy it has been found that the primary cause of death was the activation, probably by the malaria, of a tuberculous, cardiorenal or other lesion. Never-

theless, vivax malaria is a very serious entity both in civilian and military life because of the degree to which it incapacitates the patient during the acute attack and the period of several years during which relapses may be expected to occur. The subject of chronic malaria is discussed below. In Russia in recent years there has been observed a fulminating form of vivax malaria involving children and youths, manifesting grave symptoms, and terminating fatally in a few hours. According to Gontaeva, as translated by Hoare (1943), as a rule the histories of these patients point to vivax malaria during the previous autumn and to relapse attacks in the current year. This is an extremely interesting development in malariology, but it would seem that such cases would have to be observed by a number of independent investigators before one could accept the appearance of vivax malaria with such malignant propensities.

The prodromal symptoms of quartan malaria (*P. malariae*) are much like those of vivax malaria but, according to Kitchen (1941), the appearance of parasites in the peripheral circulation in almost every instance precedes the clinical onset by a few days at least. A preliminary period of remittent fever is very rarely observed in quartan malaria, the onset being intermittent from the beginning. But the infection may be of several types: the simple quartan type with a paroxysm at intervals of seventy-two hours, or the double quartan type with a paroxysm on two successive days followed by a day without fever, then two more successive paroxysms and another afebrile day, and so on, or a triple quartan in which there occur daily paroxysms, and none of these patterns may be adhered to throughout the attack. In spite of the fact that the temperature may rise no higher and the duration of the paroxysm be no longer in quartan than in vivax attacks, the quartan paroxysm is nevertheless definitely more exhausting to the patient. The spleen does not enlarge to the extent it does in vivax malaria nor does the anemia develop as rapidly, but in quartan malaria the signs and symptoms of nephrosis develop much more frequently than they do in vivax malaria. It is said that untreated quartan infection may continue clinically active for as long as nine months; when terminated by specific therapy, quartan relapses about as does vivax in the early months but it is notorious for its long duration—at least one relapse after thirty years has been recorded by a reputable malariologist. The immediate prognosis in an acute attack is about the same as in the case of vivax infection.

In falciparum malaria (*P. falciparum*) the prodromal symptoms may be about as in the other two types of malaria, but in some instances there are no prodromata at all and the patient will suddenly go into a paroxysm, perhaps even directly into coma; in fact, Kean and Smith (1944) reported that of 100 patients dying of falciparum malaria in the Gorgas Hospital in the Canal Zone over a period of years, the duration of symptoms before hospitalization varied from four and one-half hours to twenty-one days and that 23 patients had symptoms for not more than one day before hospitalization and yet they died. In most instances, however, the usual paroxysm occurs in falciparum as in the other forms of malaria though the rigor is often not very pronounced, vomiting occurs very frequently at the end of the cold stage and there is often epigastric and splenic pain. Perhaps the most outstanding feature of falciparum infection is the long duration of the fever and the nonintermittent type of the fever curve; indeed, the febrile course is of a very irregular sort because of the appearance and disappearance of cycles so that the intermittent, remittent and continuous periods combine into a completely irregular arrangement of poxyarsms. Kitchen (1941) said that it is usually possible to make out a

basic tertian cycle, but most men find it difficult to follow this pattern because of the tendency of falciparum paroxysms to anticipate or postpone in relation to the time of the previous one. The spleen does not ordinarily enlarge as much in the primary falciparum attack as it does in the first vivax attack but the degree of anemia is usually much greater; indeed, in a week of illness the patient may lose more than 2,000,000 erythrocytes and 5 Gm. of hemoglobin per 100 cc. of blood. Most feared of all, however, are the "pernicious" symptoms in this type of malaria. During the middle of War II when the Allied armies came to be much involved in malarious regions around the world, many papers appeared in which these pernicious types were described rather breathlessly and with wonderment because they were being seen for the first time by the recording observers. However, there is nothing new about all of this, since tropical practitioners have been long aware of the fact that not only may falciparum malaria involve in sledgehammer fashion many systems of the body, but also that many of these seizures will tax to the utmost the differential diagnostic skill of the most astute physician. The symptoms may run the gamut from those of the so-called "algid" type, in which the patient collapses suddenly and is found cold, practically pulseless and unconscious, through the various gastro-intestinal, respiratory and other types. The range of what may be expected I think was very comprehensively presented by Kitchen (1941), whose listing follows herewith: (*a*) *Nervous system:* hemiplegia, paraplegia, localized paralysis, epileptiform seizures, neuritis, headache, irritability, restlessness, delirium, convulsions, coma, tremors, ataxia, speech changes, aphasia, amnesia, psychoses and milder mental changes. (*b*) *Gastro-intestinal system:* syndromes of acute appendicitis, hemorrhagic pancreatitis, acute gastritis, cholera, dysentery and acute peritonitis, vomiting (bilious or hematemesis), icterus, diarrhea and melena. (*c*) *Cardiovascular and hematopoietic systems:* rupture of spleen, symptoms of thrombosis and hemorrhage, syncope, heart failure, dyspnea, hypotension, angina-like pain, anemia and leukopenia. (*d*) *Respiratory system:* pneumonia, bronchitis. (*e*) *Genito-urinary system:* syndromes of nephritis and nephrosis (albuminuria, casts), hemoglobinuria, hematuria, orchitis and oophoritis. (*f*) *Other systems:* involvement of special senses as hearing, sight (optic neuritis, retinal hemorrhage) and mastitis. Cannon (1941) expressed the consensus in explanation of these protean manifestations in saying that in benign malaria the reticuloendothelial cells in the liver, spleen and bone marrow can phagocytose parasitized erythrocytes at a sufficiently rapid rate that, while pathologic complications (infarcts, toxic changes, and so on) may take place in the liver, spleen and bone marrow, the other parenchymal organs are kept sufficiently clear of parasites that damage is not done and the patient does not die. In falciparum malaria with some one of these pernicious complications, however, the increase in the rate of production of the parasites is apparently so great that vast accumulations of them remain unfiltered out by the reticuloendothelial system and we have the relatively grossly recognizable feature of plugging of the capillaries in any part of the body, which will account for even the most bizarre of the symptoms. The studies of Knisely *et al.* (1941) and Rigdon (1944) strongly pointed toward anoxia as underlying most of the pathological alterations. Of course in untreated cases prognosis is extremely grave. The falciparum paroxysm, when it can be clearly distinguished, may last anywhere from six to thirty-six hours, but the total duration of the irregular and asymmetrical fever curve during an untreated primary attack is not likely to exceed six weeks, which

is a much shorter period than characterizes either of the other forms. Furthermore, falciparum infections probably do not persist in a latent form for more than a year, and as a matter of fact most of the relapses have occurred within six months.

Instances are accumulating in which malaria has been induced through the transfusion of blood and it would seem that under present-day methods there is no certain protection against this, for Hutton and Shute (1939), of the well-known Horton Hospital group in England, showed that all the species of plasmodia can survive for weeks at the temperature of 4° C. (39.2° F.) at which blood is stored, though it must be admitted that Antschelewitsch (1937) failed to transmit the disease in every one of 11 transfusions in which the known malarious blood had been stored more than eight days. Routine search of blood smears for organisms will not clear the donor because at most hospitals there is no one sufficiently experienced to detect the very occasional parasite in a thick film. The best safeguard would seem to be to use as donors only individuals who could not conceivably ever have become infected—a precaution which it is going to become increasingly difficult to practice in this country of ours. In the event it is foreseen that a suspected donor must be used, it is possible that if he takes atabrine for as long as is feasible before giving his blood, transmission of his latent infection may be prevented. When benign tertian has been transmitted through blood transfusion it does not relapse but both malignant subtertian and quartan do. Malaria is also transmitted by the lower class of drug addicts through the common use of an apparatus for the administration of the opiate intravenously. Most and Jolliffe (1940) reported more than 200 cases of the falciparum type admitted to Bellevue Hospital in the period 1933–1940. The first serious large epidemic of this sort in America was reported by Helpern (1934) in New York, the first anywhere by Biggam (1929) in Egypt; Chung *et al.* (1938) thought that this bizarre phenomenon occurs also in China. Black (1940) submitted presumptive evidence of the transmission of malaria during the routine administration of neoarsphenamine by the gravity method in a syphilis clinic.

Malaria in infants under ten months of age is rarely encountered but in older infants and in children up to three years of age the disease presents a different clinical picture from that seen in the adult. Periodicity in subjective and objective symptoms is absent more often than it is present, and fever is more often remittent, irregularly intermittent, or absent, than regularly intermittent and, of course, a convulsion often replaces a chill. Enlargement of the spleen fails to occur in perhaps 30 per cent of cases in infancy. Numerous cases of fetal infection through the placenta are on record, but the consensus is that such infections cannot occur if the placenta is normal, though of course it is conceivable that the malaria itself may induce such pathological changes in the placenta as to make it permeable to the parasites.

As a patient continues to experience relapses or reinfection the enlarged spleen may extend to the pelvis and it will become fibrotic and firm. This "hard" spleen often persists long after the patient has ceased to have acute attacks of malaria. The liver too may be involved; in fact in a series of 1153 cases of malaria studied by Kern and Norris (1944) during War II, probable enlargement of the liver and impaired hepatic function, both fluctuating with the activity of the disease, were observed in 60 per cent of cases in all three types of the infection. Increasingly in recent years, we are realizing that the whole of malaria is not seen when one merely observes the acute episodes during

the first year or so. It is already recognized that numerous more or less permanent residuals of a neuropsychiatric nature are chargeable against falciparum malaria, doubtless due to embolic or hemorrhagic damage during the cerebral type of paroxysm, and I imagine that in the course of years a somewhat sharper picture of chronic malaria than is now visible will be drawn, *i.e.*, we will recognize more than mere "cachexia" as characterizing this state. Indeed, experience gained in War II has fostered the description in the literature of numerous manifestations of malaria in the latent stage. For example, Talbott (1943), in addition to various central nervous system manifestations, described the following conditions as responding to antimalarial therapy alone: thyroid and adrenal gland syndromes, asthma, severe nonproductive cough, evidences of cardiac damage, pronounced pallor with a bluish or yellowish tinge to the scleras in persons who insist that they feel perfectly well, vague and various atypical pains and cutaneous eruptions. Baum (1944) described two cases in which anemia with red cell counts of 3.6 and 2.9 millions and color indices of 1.2 and 1.0 and not susceptible to treatment with iron cleared up promptly after a course of antimalarial therapy, the patients having previously had malaria. Petch (1944) also reported the case of a megalocytic anemia in an individual with chronic malaria that was cured by the use of antimalarial agents, though no parasites could ever be found in his blood; this sort of thing is familiar in the tropics, of course, but it is interesting to find such reports coming from northern countries. Zikeyev (1941) described indolent ulcers in individuals without any evidence of malaria which nevertheless cleared promptly upon the institution of antimalarial therapy; he also mentioned the case of a girl in whom skin grafting repeatedly failed until a course of antimalarial therapy had been given. Birks (1943) cited 11 cases in persons "recovered" from malaria but in whom organisms could be found at some time in the blood and whose symptoms of the following sort were all cleared by antimalarial therapy: pains in the back, rheumatic pains about joints, pains in the testicles, urticaria, multiple conjunctival ecchymosis, cardiac irregularity, recurrent diarrhea, obstinate eczematoid conditions and severe frontal headaches. Of course, it is of the utmost importance to recognize that whatever picture of chronic malaria may ultimately be drawn, the condition can arise only under two circumstances—first, in residents of endemic areas who have not yet achieved complete immunization through the experiencing of multiple attacks and second, in individuals, removed from a malarious area, whose attack of the disease had not been properly and thoroughly treated. The United States Army Medical Department took the position, in 1944, that repeated malarial relapses did not in themselves constitute a cause for discharge from the service, since experience has shown that when patients are properly cared for most of them either remain in good general condition or can be rapidly cured so that lasting incapacitation seldom results.

Malaria is extremely likely to provoke false positive Wassermann and Kahn tests, but De Groat (1943) found the new Kahn verification test reliable for the detection of these false positive reactions in his small series of cases. Rosenberg (1945) stated that the pattern of positivity in malaria, *i.e.*, positive Kahn and Mazzini tests, doubtful Kolmer and Kline tests, and the negative Eagle and Hinton tests, can usually be differentiated from that of syphilis. He said also that persistence of positive results by any test beyond six weeks, in the absence of continued evidence of malarial infection, should arouse the suspicion of syphilis. No satisfactory serological or chemical tests have been devised for

malaria itself. Failing to find the organisms in the peripheral blood or in the fluid obtained by sternal puncture, the finding of leukocytes containing pigment is considered proof of infection; confirmatory evidence is leukopenia with relative increase in large mononuclear cells (but there may even be leukocytosis!), and a deep sherry color (urobilin) in the urine in falciparum cases. During the course of an attack the blood sedimentation rate cannot be definitely correlated with the clinical findings, though Wood (1945) found that an elevated rate persists for several weeks in the majority of cases, an observation which he felt might be of value in helping to decide whether a case treated as clinical malaria really was malaria or some short-term fever. Birks (1943) found Manson-Bahr's conjunctival test a valuable one; vessels of deep red color and greater width than the normal can be seen winding a tortuous course on the surface of the conjunctiva; they are not especially numerous nor is the whole of the conjunctiva necessarily involved. It is important to bear in mind, as emphasized by Boyd (1944), that in falciparum infections the maturing parasites exhibit a tendency to recede from the peripheral to the visceral circulation as sporulation time approaches; therefore, just preceding the paroxysm the count of the organisms in the peripheral blood will be very much lower than at other times.

It is generally said that the average incubation period of malaria is ten days but perhaps fourteen would be more accurate. In the temperate zones some of the vivax infections seen in the spring and early summer are relapses but many of them are primary attacks resulting from the organism's ability to hibernate in the body during the winter (the infecting bite having occurred in the preceding autumn); in midsummer and autumn both primary attacks and relapses occur. In these zones most falciparum cases are seen in late summer and early fall. In the tropical zone infections with any of the parasites ordinarily give rise to attacks at once after the usual incubation period, but even in these torrid lands there is a seasonal periodicity of malaria not always easy to account for; the interested reader is referred to Colonel Gill's (1938) exhaustive and fascinating book on the subject. As a matter of fact, in the temperate zones we must learn to recognize the possibility of the occurrence of malaria in anyone who has ever been exposed to infection. Specifically this sort of thing may happen: an individual returning from the tropics in the winter may come down with an illness the following spring. His story to his physician would be that he had had severe malaria in the preceding summer and had experienced one or two relapses and had then completely recovered and was declared cured. The physician might then search exclusively for other diseases than malaria in his patient. This could easily cause a diagnosis to be missed, for Boyd and Kitchen (1938) showed that it is not unusual for a person multiply infected to experience falciparum attacks in the summer or fall and then have a vivax attack in the succeeding spring; Mayne and Young (1938) also showed that in mixed infections with vivax and quartan organisms one or the other of the species always predominates in much the same way. Then too, we must also become aware of the fact that unusually long incubation periods are not infrequently encountered. In the case of Boyd and Kitchen (1938), whose patient was bitten experimentally, the attack did not occur until 304 days after the bite. Shute (1939) mentioned 9 cases of protracted incubation periods averaging in length 282 days; he further noted that if the patient takes a considerable amount of atabrine after the infective bite the febrile attack may not develop until six to nine months later—this latter state

of affairs might easily obtain in many of our soldiers returning from War II. An interesting recent reference to prolonged incubation periods is that of Wilckens (1943), who reported in one of the German medical journals that 72 cases of vivax malaria were observed by him in a German field hospital near Lake Ladoga, in Russia, during April and May in soldiers who had been in the region since the preceding autumn; these cases appeared when ice and snow were still on the ground and it was impossible that infection could have taken place since the preceding autumn.

Malaria is the most important disease, infectious or noninfectious, with which mankind has to contend, for it kills more people than any other and tremendously curtails the socio-economic efficiency of those who survive. This is true even today though the incidence of the malady has greatly declined in the more northern civilized countries; experience in War II awakened the lay public to the fact already known to most physicians that it still reigns supreme throughout most of the tropical and many of the subtropical regions of the world. In the United States the disease has held sway in its time from the Gulf of Mexico to the Great Lakes (including extension well up into Canada) and from the Atlantic seaboard to well past the Mississippi River; indeed, with the beginning of extensive agriculture on the West Coast and the incursion a few years later of successive migratory waves and the horde seeking gold in 1849, malaria became established first epidemically and then endemically along our Pacific seaboard. But the recession from the north began, according to Boyd (1941), as early as the 1880's; the disease has now nearly disappeared from practically all the states north of the Ohio River, except for limited regions of benign tertian endemicity, and there seems to have occurred also a decrease in intensity even in the endemic areas where it persists in the South. Indeed, under the inspiration of Dr. L. L. Williams, Jr., Mountin (1944) of the U.S.P.H.S. proposed a program for the eradication of malaria from the continental United States, and I believe it is the consensus of malariologists that such eradication is entirely feasible.

Malaria was well known to the ancients. Garrison, quoting Blake, said that the theory of its conveyance by mosquitoes was indicated even in the Sanskrit Susruta, while another author holds it responsible for the vacillation of the Greeks before Troy. Williams (1941) said that a Chinese manuscript of the third century B.C. advised the traveler entering regions where chang-chi ("malicious air") prevailed to make arrangements for the remarriage of his widow. Hippocrates gave classical descriptions of malaria. It has been learnedly held that this ailment, by driving the population cityward, was a pronounced causal force in the final decline of the Greek civilization, and that the later Roman Empire must sooner have succumbed to attacks from the north had not the barbarian hordes been decimated by the ague. The Middle Ages knew its ravages, too, while in many a military campaign of the eighteenth and nineteenth centuries more men fell victim to chills and fever than succumbed to shot and shell. The French failure to construct the Panama Canal was due in large part to this disease, and in War I malaria was one of the chief causes of disability at troop concentration areas within the "malaria zone"; after the war the return of troops and the interchange of peoples caused its reappearance in many places long free of it: England, Germany, Russia (one of the worst epidemics in history), far up in the Arctic at Archangel. The heavy toll exacted by malaria in War II is of course known to all the readers of this book. Great numbers of soldiers returning from this war will bring latent

malaria back into the United States, but for reasons too many and complex for presentation here it is extremely unlikely that these imported cases will give rise to more than a few scattered and short-lived outbreaks. Laveran discovered the causative organism of malaria in 1880 but the modern sanitarian's attack upon the disease did not begin until after Ross, Bignami and Grassi and others in 1898 had incriminated *Anopheles* mosquitoes as the vector.

THERAPY

It seems to me that Hudson (1943) very well delineated the therapeutic dilemma in malaria when he stated that the physician is faced with two distinct types of the disease. In the first or benign type, *i.e.*, vivax or quartan infections, the patient is made very ill by severe paroxysms of chills, fever and sweat which respond somewhat sluggishly to specific therapy and are prone to relapse no matter how thorough the treatment during the primary acute attack; indeed the "cure" is really accomplished by the patient himself as he builds up his immunity during the succession of these relapses over a period of several years. In the malignant form, the falciparum infections, the patient oftentimes presents with any one of the baffling symptoms which have been listed above, but he may also appear to be not very sick at all and thus lull the unwary physician into an unjustified feeling of security; these cases, however, if promptly and efficiently treated usually respond very rapidly, are not so prone to relapse as are the benign cases, and the patient immunizes himself and thus accomplishes complete recovery much earlier than in the case of the benign form. In times gone by the attempt was made to "cure" malaria of both these types through the continuous administration of quinine to the patient over a period of many weeks, but long before the outbreak of War II the fact had been thoroughly established as a result of the investigations initiated by the Malaria Commission of the Health Organization of the League of Nations that this so-called "standard" treatment was not effective in accomplishing the desired end, and that therefore it was much preferable to use the "short-term" therapy which consists simply in treating each attack very vigorously as it occurs and recognizing the fact that it is the patient's own evolution of immunity that really effects the cure. We entered War II with two excellent specific agents—good old quinine, brought to Europe as cinchona bark in 1632 and isolated in alkaloidal form in 1820, and atabrine (quinacrine, mepacrine), a synthetic agent introduced in Germany in 1936—and we knew that these agents controlled the acute attack by destroying the asexual forms of the organism in all types of the disease and that to some extent they lessened the patient's infectiousness for mosquitoes by partial destruction of the sexual forms, though this latter action is less pronounced in falciparum than in vivax or quartan cases. But the experience of malaria in War II was so prodigious, and its codification was undertaken by men so unprejudiced, keen of mind and well-trained, that it is now possible to state in quite simple terms how one should proceed in the treatment of a case of malaria.

Choice of Drugs for Therapy of the Acute Attack.—In the Journal of the American Medical Association on the 5th of August, 1944, the announcement was made by the Board for the Coordination of Malarial Studies of the National Research Council (and a similar announcement was made by the British Medical Research Council Committee on Malaria in the Lancet of November 18, 1944) that atabrine had been fully established as the preferred drug in the armed forces and that very possibly disadvantage would accrue were

it to be replaced by quinine or totaquine. This statement was based upon vast experience which had demonstrated conclusively that atabrine is not only fully as effective as quinine in terminating a vivax attack but that it is also safer than the classical drug, and that the interval between attacks is significantly longer when atabrine has been used to arrest the paroxysm than when quinine has been employed; furthermore, there is now convincing evidence that atabrine not only terminates the acute attack of falciparum malaria but also cures this malignant form of the disease, while there is no conclusive evidence that quinine is able to perform this latter feat. Therefore, atabrine being the preferred drug, quinine is to be employed only when atabrine is not available, and totaquine is to be used only when neither atabrine nor quinine is to be had.

Modification of Therapy in Pernicious Cases.—When the patient presents with any one of the cerebral or other frank and fulminating forms of malignant malaria it is mandatory that atabrine or quinine be given parenterally at the earliest possible moment; in the report above cited it was stated that evidence is not yet at hand to decide on the relative merits of atabrine administered intramuscularly as compared with quinine administered intravenously in these fulminating cases. Some men feel that it is always well to give at least the first dose of one or other of these drugs parenterally whenever the diagnosis of falciparum malaria is made, and to me this seems a good rule, for this is a most vicious infection in which it is perfectly possible for a patient to present only the most trifling symptoms or perhaps no findings at all other than the presence of the organism in the blood and yet be dead only a few hours later as a direct result of the infection.

Anti-Relapse Therapy.—There is no convincing evidence that it is worth while treating the patient for a long period of time after atabrine or quinine has effected the subsidence of an acute attack, in the hope of preventing a relapse, but there is no reason why an individual who has learned about when to expect his relapses or who recognizes some premonitory symptom as indicating the imminence of a return of the paroxysms should not institute treatment at that time. Of course this merely amounts to beginning the treatment of the relapse before it has really become clinically apparent and does not constitute the effective prevention of a relapse. In cases in which there is an annoying amount of splenomegaly, Ascoli some years ago popularized the *intravenous use of epinephrine* (adrenalin) for the purpose of forcing large numbers of erythrocytes out of the splenic sinuses into the peripheral circulation and at the same time decreasing the size of the spleen. The method consists in giving daily intravenous injections of the drug beginning with 1/100 mg. (1 cc. of familiar 1:1000 solution contains 1 mg.), increasing to 1/90 mg. the next day, 1/80 mg. the next, and so on until 1/10 mg. is reached; this last dose is repeated daily for twenty days. The reports have been almost exclusively Italian and in them one finds both enthusiasm over the reduction in the size of the spleen and improvement in the general well-being of the patient and also complete disillusionment and disappointment with this approach. Some men give atabrine or quinine during the epinephrine course, some after it, some not at all routinely; patients previously recalcitrant to the specific drugs have been said to respond to them after the Ascoli treatment, and it has also been alleged that when this treatment is used shortly after recovery from an acute attack the subsequent relapses are remarkably mild and do not require the use of specific drugs. I should like to see a report of a thorough and unprejudiced

study of this method in some country other than Italy. The observations of Mohr (1941) and others on the Continent indicated that in malaria there may develop a considerable vitamin C deficit, both through loss and poor absorption; for methods of administering *ascorbic acid*, see Index. In Circular Letter No. 197, Office of the Surgeon General (1944), it was recognized that *vitamin supplements* such as cod liver oil and dried yeast tablets might well be given to patients who had become depressed and debilitated by long periods of relapses. Some years ago there were several enthusiastic reports upon *autohemotherapy*, but I have seen no recent reports; 10 cc. of blood is withdrawn from a vein and reinjected without added citrate intramuscularly into the buttock, giving four to seven such injections on alternate days. The injection into malarious children of *immune parental whole blood* has also been reported but it seems to me doubtful that much could be expected from this type of therapy. Many tropical practitioners feel that in the regions of heaviest infection with malaria there is also nearly always sufficient infestation with worms to warrant the use of a *vermifuge* as soon as the patient's condition warrants it. Whether *alcohol* should be forbidden the patient entirely between attacks is a moot point, but it is agreed that *excesses* of every description should be avoided, particularly *cold baths* (except during the hyperpyrexial attack) and exposure to strong *sunlight* and ultraviolet lamps, and employment in such *hot work* as that of a cook, fireman, laundryworker or the like. Only the most imperative *surgery* should be performed upon a malarious individual since operation is particularly prone to produce relapse. Of course in many instances anemia needs to be vigorously combated. Most physicians in the tropics recognize the advisability of a change of climate, the patient's resistance being increased during the sojourn in a temperate region while the parasite is dying out in his blood; since the latter occurrence requires a long time in the case of vivax infections, however, this relief measure is practicable for only the relatively few who are more or less economically independent. Though a latent malaria is extremely likely to be activated by the sudden ascent into a high altitude, such as a journey by airplane above a 10,000 foot ceiling, residence in a relatively high altitude is generally preferred for recuperation though actually this will take place just as well in any bracing northern climate.

Atabrine.—Atabrine is commercially available for oral use in the form of $\frac{3}{4}$ grain and $1\frac{1}{2}$ grain (0.05 and 0.1 Gm.) uncoated, and $1\frac{1}{2}$ grain (0.1 Gm.) sugar-coated tablets; I think the former should be preferred because they may be swallowed quickly before the bitter taste develops and there is no chance of them passing through the intestinal tract undissolved. For children the tablets may be crushed and suspended in honey or syrup; Manson-Bahr (1940) said the agent is best given to them in milk or hidden in a raisin. For parenteral use atabrine is available in ampules containing 3 grains (0.2 Gm.) packaged with 10 cc. of sterile distilled water.

Oral Administration.—Atabrine is absorbed about as rapidly as quinine but it is localized to a greater extent in the tissues and a longer time is required to attain effective plasma concentration; therefore it has been found necessary to give relatively large initial doses of this drug just as is done with the sulfonamides. In Circular Letter No. 153 from the Surgeon General's Office (September, 1943) there was stated the dosage which had proved most effective up to that time and, I may assure the reader, has continued to prove highly satisfactory up to the time of this present writing: atabrine dihydrochloride 3 grains (0.2 Gm.) and sodium bicarbonate 15 grains (1 Gm.) given by mouth

with 200 to 300 cc. of water or an equivalent amount of sweet tea or fruit juice every six hours for five doses, this to be followed by 1½ grains (0.1 Gm.) of atabrine three times a day after meals for six days, so that the patient receives a total of 2.8 Gm. in seven days. In the vast majority of cases this will suffice to effect complete subsidence of the symptoms of the acute attack, but in an occasional case the lower dosage three times a day may have to be continued for a few more days to complete the treatment.

Intramuscular Administration.—In the preamble above there were listed certain indications for the parenteral administration of the antimalarial agents; there are other instances also in which the patient cannot retain or fails to respond to the atabrine given by mouth. In all of these cases the intramuscular route is preferred: Atabrine dihydrochloride, 3 grains (0.2 Gm.) in 5 cc. of sterile distilled water, is injected intramuscularly with the usual precautions into each buttock, giving a total dose of 6 grains or 0.4 Gm. If necessary, 1 or 2 additional doses of 3 grains (0.2 Gm.) may be given intramuscularly at intervals of six to eight hours. As soon as the patient can take and retain oral medication, atabrine should be given by mouth in such doses as to give a total by both routes together of 15 grains (1.0 Gm.) in forty-eight hours, followed by 1½ grains (0.1 Gm.) three times a day after meals for five days (total, 2.8 Gm. in seven days).

Intravenous Administration.—There is a general impression that atabrine should not be given intravenously—Hudson (1943), for example, unreservedly condemned this intravenous employment because of the alleged proximity of the therapeutic and toxic doses—but I am not myself convinced that the drug is so highly toxic when given by this route and should like to see the report of its thorough trial.

Dosage for Children.—In 1940, Manson-Bahr recommended the following daily dosage for children: up to one year, ¾ grain (0.05 Gm.); from one through four years, 1½ grains (0.1 Gm.); from five through eight years, 3 grains (0.2 Gm.); from eight upwards the adult dose of 4½ grains (0.3 Gm.). But as will be seen from the adult dosage here stated, this dosage for children was promulgated before the lessons learned in War II with regard to the advisability of higher dosage in adults. I have seen no published dosage scheme for children in which the new higher dosage was employed, but I should think that since children tolerate this drug well Manson-Bahr's dosage might safely be increased in all the age groups in the beginning of a fulminating infection in the child just as is done in the adult (see above).

Toxicity.—Atabrine is yellow and causes the urine to assume the same color on about the third to fifth day (the first indications of this may be had by adding a few drops of acetic acid, heating and looking down the test tube against a black background); in many instances yellow discoloration of the skin (but rarely of the sclerae) also occurs. This discoloration is entirely due to the acridine dye nature of the drug and not to jaundice indicative of liver injury; it usually disappears in one to two weeks, though persistence for several months is on record and patients are perhaps well advised to keep out of direct sunlight for a month following an atabrine course to lessen the likelihood of this occurring. Other annoying, but neither serious nor very frequent, symptoms are headache, abdominal pain, nausea and diarrhea, any of which is likely to last for several days after the drug is discontinued; in the study of Loughlin *et al.* (1943), in which large numbers of the personnel of a number of hospitals were given the drug in prophylactic dosage, all the healthy

subjects were able to carry on assigned duties during the period of medication. Parrot *et al.* (1943) said that the administration of atabrine to small infants by spoon frequently provokes immediate vomiting, but I do not imagine it would be very likely to do so if suspended in honey or syrup, or given in the milk as suggested by Manson-Bahr. Atabrine does not cause visual or aural disturbances and is usually preferred to quinine by the patient who has had experience with large doses of the latter; I have heard individuals say that they were actually stimulated by the drug and others have reported the same thing, but I am frankly skeptical of the occurrence of this effect

In a low proportion of cases (but with reports from all over the world so that there can be no question of a social predisposition) actual psychoses have been caused by the drug; they have been usually mild and transient affairs, but some patients have presented wild manic states gradually merging into somnolent delirium and even deep coma lasting several days to a week. Permanent derangement has not been reported. Govindaswany (1940) in a deliberately performed study found that certain types of mentally deranged individuals, as well as alcoholics (Whittingham, 1939, agreed here) and arteriosclerotics, do not tolerate the drug well. Choremis and Spiliopoulos (1938) noted peculiar paralytic residuals in a small number of children. Experience in the Ceylon malaria epidemic of 1934–35 showed, according to Fernando and Wijerama (1935), that atabrine should not be given in cases of advanced hookworm disease or where there is disturbance of renal function; Wickramasuriya (1937) agreed. Van Heukelom and Overbeek (1938) would have the drug used with great caution if there is jaundice or evidence of liver damage. However, McCorkle's (1944) study of the liver function test in 55 selected patients, during War II, indicated that atabrine's effect upon liver function as measured by the hippuric acid test is insignificant; all his patients had had at least four months of 0.6 Gm. of atabrine weekly and 79 per cent of them had had at least four intensive courses of the drug during relapses. Agranulocytosis has been reported and a few cases of hemorrhagic disturbance of the blackwater fever type (Field *et al.*, 1937, considered advanced anemia to be a contraindication), and at least one case of exfoliative dermatitis presumably but not certainly caused by the drug (Holton, 1938). Atabrine may apparently be safely used in any stage of pregnancy, though Wickramasuriya probably expressed the consensus in stating that he would have it withheld in pregnancy toxemia.

The above listing seems a quite formidable array of toxic reactions but as a matter of fact most of the serious ones are of rare occurrence. Bispham (1941), of the United States Army, studied the reported reactions in 49,681 cases in which atabrine had been given, 7915 of the cases having been seen by himself. It is true that in a large proportion of instances the drug had been used only in prophylactic dosage; still it seems significant to me that it had caused a severe reaction only 38 times. Figures on the number of severe reactions which occurred in the Army and Navy during War II have not yet been published but it is known that the incidence was extremely low. There certainly seems to be no doubt that in routine short-course therapy or in prolonged prophylactic use of the drug the majority of individuals are much less disturbed by it than they would be by quinine.

Quinine.—The least expensive and most used salt when quinine is available is the sulfate, given in capsules or tablets. The hydrochloride or the dihydrochloride or the alkaloid itself may be used in the same dosage as quinine sulfate,

but any of them is more expensive and no better than the sulfate. All of these drugs are relatively insoluble, but if the capsule opens or the tablet is held more than a moment there will arise nevertheless an intensely bitter taste in the mouth. There is strong temptation to prescribe ready-made chocolate or otherwise coated pills, but these are often stony hard and may pass through the intestinal tract undissolved. Quinine ethyl carbonate (euquinine) is so insoluble as to cause little taste and is much given to children in the same dosage as the sulfate; it is considerably more expensive. There has always been disagreement regarding the proper dosage of quinine tannate, another insoluble salt, and it has been omitted from the U.S.P. Quinine bisulfate is sufficiently soluble that it may be prescribed in solution, but it has a lower alkaloidal content than the other salts and should be given in one-third larger doses—about 13 grains (0.8 Gm.) of the bisulfate instead of 10 grains (0.65 Gm.) of the sulfate. The following prescription is about the best that one can do in the way of disguising taste (and little enough it is!):

℞ Quinine bisulfate..... ʒiiiss 14.0
Aromatic syrup yerba santa (eriodictyon) to make..... ℥iv 120.0
Label: As directed. (A teaspoonful contains the *equivalent* of about 5 grains [0.3 Gm.] of quinine sulfate.)

In American military circles the pleasant little custom used to prevail of bringing the sulfate into simple unflavored solution in water by the addition of concentrated hydrochloric acid at the rate of 1 drop of the acid and 5 grains of the salt to a drachm of water. This barbarism is best not attempted in civilian practice. Of course there are hoards of expensive quinine solutions and suspensions on the patent medicine shelves and they are much resorted to by patients who are superior to medical advice. As an ethical preparation the Council on Pharmacy and Chemistry has accepted the Coco-Quinine of Eli Lilly and Company, a chocolate, vanilla and yerba santa flavored suspension containing 10 grains (0.65 Gm.) of quinine sulfate per ounce. This Coco-Quinine is somewhat expensive, of course, but it is a splendid preparation to use in children if there is difficulty in getting them to take the drug disguised as in the above prescription; or one may try the method suggested by Reed (1940): dissolve 5 grains (0.3 Gm.) of quinine dihydrochloride in 4 teaspoonfuls (15 to 20 cc.) of water and add a little honey, syrup or jelly—one-fourth of the solution will contain about 1¼ grains (0.08 Gm.) of the drug.

Oral Administration.—In the standardization of dosage by the Surgeon General's Office (see above under *Atabrine*), it was stated that if atabrine is not available quinine sulfate should be given by mouth in dosage of 15 grains (1 Gm.) three times a day after meals for two days, following this by 10 grains (0.6 Gm.) three times a day after meals for five days (total 16 Gm. in seven days). I think it should be noted here, however, that Hiatt (1944) found the plasma concentration of any of the alkaloids of quinine markedly lower if the drug is taken immediately after a meal. Through Campbell (1942), the National Research Council approved the following "minimum" daily dosage for children: under one year, 2½ grains (0.16 Gm.); one to two years, 5 grains, (0.32 Gm.); three to four years, 7½ grains (0.48 Gm.); five to six years, 10 grains (0.65 Gm.); seven to eight years, 12½ grains (0.81 Gm.); nine to ten years, 15 grains (1.0 Gm.); eleven to twelve years, 17½ grains (1.16 Gm.); thirteen years and over, 20 grains (1.32 Gm.). The Council stated at the time of the above pronouncement that the adult dosage of 20 grains instead of the optimum of

30 grains was specified merely as a compromise to provide for a possibly effective dose and to conserve the stocks of quinine alkaloids during the war period; it must be recalled to the reader's attention that at the time the superiority of atabrine to quinine had not yet been established and there was serious concern over our ability to handle the therapy of malaria should the quinine stock be exhausted.

During War I and to a less extent during War II reports appeared of quinine-resistant malaria, but Hughes and Murgatroyd (1943) found what Fletcher had discovered in the earlier war, that when the patient is actually seen to swallow the quinine in the presence of the physician the alleged "resistance" disappears. Nevertheless, Howie and Murray-Lyon (1943) found that despite precautions to insure that quinine was being regularly taken, 24 out of 100 malaria patients showed negative Tanret reactions in all or many of their urines during treatment and convalescence, their responses to quinine therapy comparing unfavorably with those whose Tanret reactions were regularly positive; so it would seem that quinine absorption from the gastro-intestinal tract under almost all circumstances does not perhaps occur with as great regularity as had been thought.

Intravenous Administration.—When one of the indications for parenteral administration of quinine exists (see discussion in preamble above), the preferred route nowadays is intravenous, at least the employment of that route only was apparently countenanced in the armed forces during War II. The official method of giving the drug consists in the administration of 10 grains (0.6 Gm.) in 300 to 400 cc. (the absolute minimum being 200 cc.) of sterile physiologic saline solution, injecting with the usual aseptic precautions and *especially avoiding speed.* If necessary in emergencies there should be no hesitation in cutting down upon the vein. This treatment may be repeated in from six to eight hours if the situation demands it. When the patient can take and retain oral medication he should be given a complete course of atabrine if it is then available or otherwise quinine, dosage in either case being that previously stated for the oral administration of these drugs. There are many men who throw their hands up in a gesture of holy horror at the mere thought of administering quinine intravenously, but as a matter of fact it seems that experience in War II proved that the measure is fully justified where the proper indications exist and that it is not excessively dangerous—testimony on both sides of this highly controversial question is so voluminous that I cannot take up the space here to cite it. Most and Meleney (1944) stated that since rapid intravenous injection of quinine may produce a definite fall in blood pressure it is well to have at hand a sterile syringe containing 1:1000 epinephrine solution, of which 1 cc. may be slowly given intravenously in the event collapse occurs. I have heard it stated that the fall in blood pressure is less if the quinine is administered in blood plasma instead of in saline solution, but this so far as I know is only a rumor. Since intravenous administrations of quinine have undoubtedly been life-saving many times, I do not see why it would not be feasible to institute a slow intravenous drip therapy in many cases of falciparum malaria. Smith and I (1944) showed that something approximating this method was remarkably efficacious in experimental infections and I should like to see something of the sort given a clinical trial.

Intramuscular Administration.—Opinion vacillates so much with regard to the admissibility of the intramuscular administration of quinine salts that it is difficult to make any statement of its current status which may be accepted

as at all authoritative, though there is no blinking the fact that no mention of this method of administration was made, so far as I am aware, in the directions to the armed forces during War II. Of course the objection to the method is based upon the alleged frequent occurrence of severe abscess at the site of injection, but there are many men of vast experience who claim that they do not see these abscesses though they have used intramuscular injections routinely in thousands of instances through the years. It seems to me rather amusing that Hill and Howie (1942) were able to remind us that Rogers pointed out many years ago that cinchonism appears more slowly after intramuscular than after oral administration of quinine, the inference being that the former is actually the most gradual means of giving the drug since local necrosis delays absorption; and indeed Lowe (1944) stated that the preliminary findings in a study of this matter at the School of Tropical Medicine in Calcutta indicated that intramuscular quinine is little if any more effective than the same dosage given by mouth. Nevertheless, the late Warrington Yorke (1942), while admitting that only a small portion of the drug is absorbed, having himself found considerable quantities in the muscles of experimental animals weeks after injections were made, stoutly championed the intramuscular route as the result of twenty-five years of experience with it; he said he was sure that it had saved very many lives and that he had never seen the dire results so dolefully listed by many observers.

Quinine dihydrochloride used to be the preferred salt but it is now recognized that its high acidity contributed toward the dangers of this procedure and it is being replaced by the simple hydrochloride, rendered more soluble by the addition of urethane or antipyrine. One can easily prepare the solutions according to one of Winckel's (1940) formulae:

℞	Quinine hydrochloride	gr. x	0.6
	Urethane	gr. v	0.3
	Water to make	ʒss	2.0

℞	Quinine hydrochloride	gr. x	0.6
	Antipyrine	gr. v	0.3
	Water to make	ʒss	2.0

These solutions must of course be sterilized by boiling and then cooled to body temperature before use; or larger quantities may be stored in rubber capped bottles, the top being wiped thoroughly with alcohol before each withdrawal and the contents resterilized each week. It seems to me these solutions are too concentrated; *i.e.*, 5 grains (0.3 Gm.) of the quinine salt to 1 cc. Williams (1940) placed 5 grains in 5 cc.; I would therefore suggest the following formula:

℞	Quinine hydrochloride	gr. x	0.6
	Urethane or Antipyrine	gr. v	0.3
	Water to make	ʒiiss	10.0

Label: Sterilize by boiling and when cool inject 1 cc. for each 1 grain (0.06) of quinine desired.

However, I think I should add that McGuire *et al.* (1943) found that quinine sulfate can safely replace quinine dihydrochloride for intramuscular injection when the solution is prepared as follows: 100 grains (6.5 Gm.) of quinine sulfate are dissolved in 10 cc. of distilled water to which 100 minims of official dilute hydrochloric acid have been added, further distilled water then being added

to bring the total quantity up to 20 cc. The solution is filtered through moistened filter paper, boiled, kept in a sterile rubber capped or stoppered bottle; it may be reboiled if necessary. One cubic centimeter of the solution contains 5 grains of the sulfate, and injections of it were said by McGuire *et al.* to be no more prone to produce abscess formation than injections of the dihydrochloride; indeed, they reported the giving of about 6000 injections in the preceding twelve months without any abscess formation, even infants a month old being treated with this preparation.

In injecting quinine intramuscularly it is important that the needle without any solution in it be introduced first and then the syringe attached, and that at the conclusion the quinine syringe be replaced with one containing a little air or sterile water to be injected to clear the needle of solution before it is withdrawn. These injections must be made slowly and at their conclusion the area is to be gently massaged for ten minutes.

The same amount of drug and at the same intervals may be employed intramuscularly as by mouth but it is often found that after the first injection (10 to even 15 grains, 0.6 to 1.0 Gm., may seem indicated in some fulminating cases) the subsequent doses can be considerably reduced. Of course the objective is to save the patient's life and then to get him on to oral administration; this is usually accomplished in a few days.

Rectal Administration.—For the adult, 30 grains (2 Gm.) of the dihydrochloride may be dissolved in 1 quart (1000 cc.) of normal saline and given by rectal drip during twenty-four hours; 2 ounces (30 Gm.) of dextrose added to this will enable one to supply specific drug, nourishment, fluid and salt to a patient dehydrated by continuous vomiting. For the preparation of a retention enema if a soluble salt of quinine is not available and the sulfate must be used, Manson-Bahr (1936) directed that the drug be dissolved with the aid of tartaric acid to avoid making the solution irritant; hydrochloric acid will necessitate such dilution as to make it difficult for the enema to be retained. In children having convulsions, which is the counterpart of the cerebral form of pernicious malaria in the adult, he advised heroic dosage: 5 grains (0.3 Gm.) in a one-year-old child, followed by half this quantity every hour until convulsions cease. In these children the buttocks will often have to be pressed together to ensure retention; normal saline or thin mucilage are better solvents than plain water.

Toxicity.—On the now outmoded long-course "standard" method of treatment with quinine it was not unusual for patients to be made very uncomfortable by one or more of the following symptoms: nervousness, headache, giddiness, palpitation, tremors, nausea, disturbances of sight and hearing. Sodium bromide, 2 grains (0.12 Gm.) for every 1 grain (0.06 Gm.) of quinine, was often given to control these symptoms. Even under the newer short-course intensive treatment these symptoms frequently occur and constitute a very serious objection to the use of the drug. Occasionally loss of sight and hearing have occurred and return of complete function has not always taken place upon cessation of the administration of the drug; however, such serious poisoning occurs very rarely. Idiosyncrasy is quite another matter, however, for patients truly hypersensitive to the drug may be upset by very small doses. The most usual signs of idiosyncrasy are skin rashes, gastro-intestinal disturbances, coryza, pseudo-asthmatic and anginal phenomena; purpuric and other hemorrhagic disturbances (including the blackwater fever type of syndrome) and agranulocytosis have been reported, and since this is an allergic type of

reaction almost anything can be expected. The substitution of quinidine for quinine in cases of idiosyncrasy to the latter drug has been shown—principally by Sanders (1930–1936) and his associates—to be feasible. In their experience there were only a few instances of separate idiosyncrasy to quinidine.

It is alleged that quinine taken during menstruation will diminish the flow or increase it if there is a tendency toward menorrhagia; however these things are not established and not taken into account when the drug is imperatively needed. Traces have been detected in the milk but they are insignificant as regards effect upon the suckling infant. Balasquide (1939) stated that there is a general belief in Puerto Rico that quinine dries the maternal secretions but he knows this to be unfounded. Regarding pregnancy, it is established that extensive infection of the placenta with the falciparum parasite is very likely to cause the death and premature expulsion of the fetus; Blacklock and Gordon many years ago found that more than a third of the placentae of West African native women examined by them contained large numbers of organisms, and that 25 per cent of the children of these women died within a week. It is agreed by all observers also that malaria of any type may lie dormant until awakened during labor, at which time the first typical pyrexial attack may occur. So much for the undoubted effect of the disease upon the pregnant woman, but of the effect of quinine upon her there is a difference of opinion. In some parts of the Far East the feeling is widespread, and apparently fostered by European practitioners, that periodical dosage with quinine predisposes to abortion. Thus Manson-Bahr states that he has treated pregnant patients at term who were suffering from advanced malarial cachexia but had been strictly forbidden by their medical attendants to take quinine in any form; his own feeling is that pregnancy does not contraindicate the use of the drug altogether but that the minimum dosage likely to be effective, "say 3 grains (0.2 Gm.) repeated every eight hours for two days," should be employed. Wickramasuriya (1937), who gave much attention to this matter in Ceylon, became convinced that full quinine dosage should be given and that the concomitant use of bromides holds the oxytocic action of quinine fully in abeyance; indeed he has known this treatment in many instances to prevent abortion which seemed imminent under the influence of malaria. Balasquide, in Puerto Rico, also felt that the drug is not contraindicated. Interestingly, Smith, in the United States, a few years ago reported satisfactorily upon the employment of $1\frac{1}{2}$ grains (0.1 Gm.) three times daily for three weeks prior to expected confinement in 60 presumably nonmalarious women for what he considered its general tonic effect.

One other thing needs to be mentioned, however. It seems that quinine given to the pregnant woman is capable of causing serious visual and aural disturbances in the infant; this has occurred extremely rarely to be sure, but it has occurred (see Taylor, West, Richardson and Forbes, in the Bibliography).

It is heralded as one of the great advantages of atabrine that it may be more safely used than quinine in pregnancy, but Wickramasuriya says it would appear that the drug is contraindicated in the toxemias of pregnancy.

Totaquine.—During the early part of War II, when Java, the source of quinine, had been lost and the superiority of atabrine to quinine had not yet been established, the U. S. Pharmacopoeia recognized the brown insoluble powder known as totaquine, which by definition contains not less than 7 and not more than 12 per cent of anhydrous quinine and a total of not less than

70 and not more than 80 per cent of anhydrous crystallizable cinchona alkaloids, these latter including cinchonidine, cinchonine, quinidine and quinine. This definition permitted the use of Latin American cinchona barks which are relatively low in quinine content. Somewhat similar totaquine had been in use for many years in various parts of the world where the attempt had been made to supply a relatively cheap form of antimalarial drug for pauper native populations, and it has been the consensus that it is very effective in the treatment of the disease; indeed some observers have claimed for totaquine a greater value than for quinine. Witness the report of Wijerama (1939), who treated 95 patients with totaquine and 132 with quinine bisulfate, some receiving 15 grains (1.0 Gm.) and some 20 grains (1.3 Gm.) of either drug daily; there were 127 falciparum, 59 vivax, 10 quartan and 31 mixed infections. Totaquine proved the more effective in stabilizing temperature, causing the disappearance of parasites and inhibiting the formation of gametocytes in all three types of the disease in this study. The most extensive study of American totaquine was that reported by Green (1945) in which, at a hospital in a foreign theater of war, 80 cases of malaria of all three types were treated with totaquine, 80 with quinine and 80 with atabrine, the quinine and atabrine both being employed in the official dosage of the S.G.O. Circular Letter No. 153 (see oral methods of administration of both of these drugs above), and the totaquine in the same dosage as the quinine. Totaquine controlled fever in a period of time identical with that of quinine and caused the disappearance of organisms from the blood stream in practically the same length of time as the older drug; incidence of toxic symptoms was about the same for totaquine and quinine, but the nausea and vomiting caused by totaquine proved more disagreeable than any toxic symptoms of either quinine or atabrine. The interval between attacks and subsequent relapses was shortest for cases treated with totaquine and slightly longer for cases treated with quinine. Cases treated with atabrine relapsed at intervals which on the average were three times as great as the intervals following totaquine therapy.

Quinidine.—Of the several alkaloids of cinchona bark other than quinine, the one which has had the most extensive clinical study is quinidine, though the findings of Sanders and his associates in Louisiana with this agent have really not been confirmed by other workers elsewhere. In 1942, Sanders reported on a cooperative study of quinidine with other physicians in Louisiana in which 1449 quinine-treated cases were compared with 2215 quinidine-treated cases, the conclusion having been drawn that the agents were equally effective. A few only of Sanders' patients complained of weakness shortly after taking the drug but this did not recur when they were asked to stay in bed for an hour after taking it. Some complained of nausea but this may have been attributable to malaria as well. There were a few instances of idiosyncrasy as with quinine but the drug was also used satisfactorily to replace quinine in instances of idiosyncrasy to the latter. In ordinary routine therapy quinidine seemed to cause less tinnitus and nervousness than the classical drug. Some years ago Sanders reported a series of 32 pregnant women in all stages from the first to the ninth month who were treated with quinidine without any ill effects upon either mother or infant.

Plasmochin (Pamaquine Naphthoate).—This drug was formerly used after completion of the course of atabrine or quinine in the attempt to prevent relapses, but experience in War II amply showed that it was ineffective when used for this purpose and furthermore that it caused so much discomfort

that even had it been somewhat effective its use would have been doubtfully justifiable. I shall therefore devote no further space to a consideration of plasmochin.

Organic Arsenicals.—Following War I there was quite a flurry of interest in the use of the arsenicals. Stephens *et al.*, of the Liverpool School of Tropical Medicine, used single intravenous injections of neoarsphenamine in doses varying from 0.45 to 0.9 Gm. and found that they were often able to control the febrile paroxysms and cause the disappearance of parasites from the cutaneous blood in about twenty-four hours in vivax cases; however, from the standpoint of prevention of parasitic relapses the effect of these injections was practically nil. They then undertook the study of inorganic arsenic and found that when used alone, this agent (Fowler's solution) was not effective in vivax cases, but when used in doses as high as 2 cc. (30 minims) daily in conjunction with regular quinine dosage, there seemed to be a reduction in the incidence of relapses. This same group of workers then reported neoarsphenamine to have no value in falciparum and in quartan cases. They then returned to the study of Fowler's solution, for having found it somewhat effective in reducing the relapse incidence when used in large daily dosage over a period of eight weeks in combination with two initial intramuscular injections of quinine dihydrochloride on two days only, they sought to determine its effectiveness when used in the same daily dosage for sixteen days with an intramuscular injection of quinine on the first, second, eighth, ninth, fifteenth and sixteenth days. They found it impossible to make an acceptable analysis of their data. The next publication of note was that of Pratt-Johnson *et al.* (1921), of the British Army, who, as a result of their investigation, recommended three or four weekly injections of neoarsphenamine in conjunction with quinine treatment, but stated that freedom from relapses cannot be promised even after numerous intravenous injections. Then, in 1924, Col. Clayton Lane, making a critical review of the treatment of the malarias for the Tropical Diseases Bureau in England, stated "neoarsphenamine, so far from being curative in falciparum malaria, has been in a number of cases the cause of death, lighting up a malaria latent and recognized too late. On vivax malaria its immediate effect in suppressing parasites is generally marked, yet relapse has constantly been reported." Then, in 1925, Commander Wittingham of the R.A.F. Medical Service read a paper before the Royal Society of Medicine in which he stated his belief that in the treatment of vivax malaria neoarsphenamine compared very favorably with quinine. He said, "The drug is not recommended in the treatment of malaria to the exclusion of quinine, but should be used in conjunction with it to ensure that the patient receives enough treatment to prevent a relapse." The two men who discussed this paper did so adversely. Powell said that when neoarsphenamine first came into use he had employed it with high hopes in malaria, but had found no reduction in fever or number of relapses and little diminution in the number of parasites in his cases. Furthermore, in frequent instances he had seen malarial attacks begin in patients who were receiving the arsenical drugs for the treatment of syphilis at the time. Colonel MacArthur said he considered the arsenical preparations had little direct action on the malaria parasites. His experience had also been that malaria would develop in persons undergoing active neoarsphenamine treatment for other conditions, and he cited a dozen cases of individuals who were actually infected with malaria—several of them fatally—by an injection of neoarsphenamine given through tubing contaminated with

blood from a malaria carrier who had received an injection previously. A freshly sterilized needle had been used for each person but the same tubing had been employed throughout. (More recent cases of this sort are on record.) Colonel MacArthur stated that he could not imagine such infections occurring through a similar action during intravenous administration of quinine. He did not deny some value to the arsenicals but believed the beneficial effects were due to the tonic properties of the preparation and not to any direct parasiticidal action.

In more recent times, Goldman, in 1938, used mapharsen to terminate attacks of induced vivax malaria with "strikingly good effect." Nine of his patients received 11, one received 4, and fourteen patients received 1 intravenous injection of 40 to 60 mg. of the drug. There were only two relapses and both of these occurred after the patients had received only one injection of mapharsen. Goldman stated that this drug was immeasurably more effective than quinine for the treatment of malaria. However, Cleveland and Turvey, in 1939, also treating vivax inoculation malaria, felt that if mapharsen is to be used to supplant quinine as a means of terminating this type of malaria, a full course of injections should be given, for experience has shown that when the malaria appears to have been cured it may have been only temporarily arrested. Young and McLendon, of the U. S. Public Health Service, in the same year, found mapharsen ineffective in the control of induced quartan malaria. Winckel, studying the matter in Amsterdam in 1941, found that intravenous injections of neoarsphenamine constitute a simple means for either changing a double fever into a simple one or for allowing the patient a few afebrile days. However, he felt that neoarsphenamine could not replace quinine in the treatment of malaria, stating "for definitely cutting short the fever course, after the inoculation by the injection of blood, 5 Gm. of quinine sulfate in five days is required and is sufficient; clinical relapses are not encountered." The most recent authoritative study is that of Lowe, professor of tropical medicine at the School of Tropical Medicine in Calcutta, who, publishing in the Indian Medical Gazette in March, 1944, concluded: "Though the number of cases treated was not great, it was not considered justifiable to continue this line of investigation further. The experiment indicated clearly that the use of these two arsenical preparations (neoarsphenamine and mapharsen) in the treatment of malaria had severe limitations. They could only be used with safety in cases in which one was quite sure that one was dealing with a pure *P. vivax* infection. Our experience in Calcutta is that one can very rarely be sure of this. Even if one could feel sure and applied the treatment with either of these preparations, the relapse rate would still be considerable. It is therefore clear that neither of these preparations can be recommended for wide use in the treatment of malarial fever. It is however not impossible that a combined treatment of one of these preparations with quinine might be a very effective treatment for malaria and that the relapse rate might be considerably reduced. We have no definite evidence on this point and are not at present in a position to study the matter."

Now just as this book goes to press, evidence of the sort desired by Lowe (above) has become available, for Kay (1945) treated alternate cases of relapsing vivax malaria in American soldiers in the Far East with atabrine plus mapharsen or with atabrine alone; of the 67 treated with atabrine and mapharsen 71.6 per cent relapsed, while of the 109 treated with atabrine alone 74.3 per cent relapsed. It is therefore apparent that mapharsen is of

no value as an adjuvant to atabrine in the treatment of relapsing vivax malaria.

Bismuth.—In 1943, Young *et al.* of the U.S.P.H.S., confirming the earlier findings of Schwartz (1938), failed to find that thiobismol in 0.1 or 0.2 Gm. amounts had any effect against quartan or falciparum cases, but they did find that it had an inhibitory effect against vivax parasites which were half grown, about sixteen to twenty-four hours after the last paroxysm caused by that group of parasites. Parasites older or younger were not affected. By so using the drug, they changed the occurrence of paroxysms from daily to every other day and thus enabled their neurosyphilitic patients better to undergo a full course of malaria care. For the termination of vivax infections they found that one injection of thiobismol given the day quinine is started usually acted better than quinine alone by preventing a paroxysm the following day, and they suggested that this combination might find a wider use generally.

Nursing, Diet and a Few Special Measures.—It seems to me very important to emphasize to practitioners in the temperate zones where malaria is likely to be increasingly seen under present world conditions that this is a serious disease and not to be treated lightly merely because it bears the unimpressive soubriquet "chills and fever." During the paroxysm the patient will put himself very miserably to *bed*, but the point is that he should be required to remain there until adequate use of one of the specific drugs has assured that the acute attack is over. Every effort should be made to try to mitigate his *discomfort* during the chill stage and when he is sweating the bedclothes and his night clothing need frequent changing. In Puerto Rico, Stevenson (1944) administered 10 cc. of a 10 per cent solution of calcium gluconate intravenously very slowly in 50 patients just after onset of the chill; the procedure was at times difficult to carry through because of the uncontrollable shaking of the patients, but it was reported that a complete termination of the phenomenon within one to three minutes occurred in most cases. The ordinary analgesic and antipyretic drugs are perhaps hardly worth using during the fevered stage, but if *hyperpyrexia* develops the cold pack must be employed; Manson-Bahr (1940) stated it as a good rule to put the patient in the pack when the axillary temperature reaches 106° F. (about 41° C.) and remove when the rectal temperature is 102° F. (about 39° C.).

During the acute attack of benign tertian or quartan the *diet* presents no problem for the patient even if not vomiting is unlikely to desire more than the lightest food; return to full diet after the paroxysm may be rapid. Mirsky *et al.* (1944), finding evidence of hepatic damage in 10 carefully studied cases of both falciparum and vivax forms, proposed that in addition to the specific drugs a high carbohydrate, high protein and high vitamin diet be administered early in the therapeutic regime. Sinton in his vast experience found that vomiting may be remarkably well controlled by the oral administration of 20 minims (1.3 cc.) of epinephrine solution; morphine is often given. To combat dehydration large quantities of physiologic saline solution, preferably with the addition of 5 per cent of dextrose, will have to be given; in the Circular Letter from the Surgeon General's Office, frequently referred to in this article, it was advised that when dextrose is administered in this way it should be supplemented with 1 mg. of thiamine hydrochloride (vitamin B_1) for each 25 Gm. of dextrose. Latterly blood and plasma transfusions have also been much employed, though I have not as yet seen a report in which their value was definitively shown. Lipscomb (1939), following Sinton, advocated the use of alkalis

in the hope of preventing blocking of the tubules of the kidneys by liberated blood pigment. If an attack of the cerebral type is threatening, ice-bags are frequently applied to the head and to the feet. It is said that the inhalation of amyl nitrite may make the parasites more accessible to the specific drugs through dilatation of the vessels, but I much doubt the wisdom of this therapy; however, Most and Meleney (1944) stated that in their opinion it might be advisable to administer 100 mg. of nicotinic acid (not nicotinic acid amide) every hour intravenously to maintain the cerebral capillary vasodilatation—they cited a case, indeed, in which this procedure restored consciousness immediately. Most and Meleney also said that sometimes spinal drainage may restore the patient to consciousness. In a small group of cerebral cases whose mania was so wild that the individuals could not be easily handled in order to institute specific therapy, Gillett (1944) began his treatment by giving pentothal intravenously as for an ordinary surgical procedure, the patients being forcefully restrained for the few moments required to make the injection. To the author's surprise the patients remained deeply asleep for many hours after the dose of pentothal and upon awakening seemed to have obtained exceptionally beneficial results from the specific antimalarial agents that had been administered in the interim.

SUPPRESSIVE TREATMENT (DRUG PROPHYLAXIS)

In the current state of our knowledge the following attempts at prevention of the disease through the use of drugs might logically be made.

Mass Treatment.—By this I mean making monthly parasite surveys of an area and treating all the positives with drugs in the hope of greatly reducing transmission in the area. It does not succeed, as was shown conclusively by Clark and Komp in their thoroughgoing ten-year study (1931–1941) in Panama. They did not even succeed in preventing epidemics when unusual numbers of mosquitoes were present; but they were successful in reducing cases of severe clinical malaria in the region almost to the vanishing point.

Plasmochin.—One would think that the administration of this drug of demonstrated gametocidal properties to the entire population of a given malarious region would practically prevent mosquito transmission of the disease in that region, and it is faintly possible that it would—but I cannot conceive of any public health official of sound mind undertaking such a gargantuan project. Even reduced to theoretically attainable proportions, *i.e.*, the administration of the drug to demonstrated carriers only, the method is impracticable. Earle and Perez' (1936) study in Puerto Rico showed this; for three years from 30 to 40 children (the most important gametocyte carriers) in an endemic center were kept under continuous observation, the malaria parasites being counted once a week or more frequently when fever was present or numerous gametocytes were found. The only admissible conclusion from their work was that there is no way of predicting the presence of gametocytes in the blood stream and, therefore, that in order to keep check upon those who are and those who are not carriers at a given moment in any region blood smears would have to be made of the entire population at impossibly frequent intervals.

Causal Prophylaxis.—There is not as yet available any agent which will effect true causal prophylaxis by destroying the sporozoites injected by the mosquito—and that is that!

Suppressive Treatment.—What remains is simply the attempt, under the title of "clinical (in the sense of practical) prophylaxis," to maintain sufficient

concentration of the specific drugs, atabrine or quinine, in infected individuals so that the asexual forms of the parasites which they harbor cannot cause severe symptoms and the sexual forms are reduced sufficiently that infectiousness for mosquitoes is much decreased. It was this type of suppressive treatment which proved so valuable in War II.

Atabrine.—That atabrine proved a more suitable drug for suppressive treatment than quinine during the war was amply evidenced by the praise of the drug that appeared in all official reports and the fact that at the time of this present writing it is being used almost to the exclusion of the classical agent, but the only large-scale study supplying statistical evidence of atabrine superiority which has as yet come to my attention is that of Findlay and Stevenson (1944) from the Gold Coast of West Africa; such reports may be expected to appear in large numbers after the termination of hostilities. The method of employing atabrine which seems to have found highest favor is the taking of a tablet of 1½ grains (0.1 Gm.) once daily at the evening meal for six days each week. This of course turns the individual a nice yellow color after a time but it does not very often cause gastro-intestinal disturbances and when it does these disturbances usually disappear if the taking of the dose is persisted in for a few days. Experiments employing soldier volunteers have shown conclusively that the level of atabrine concentration in the blood is not lowered by excessive perspiration. Since with this suppressive dosage the maximum plasma concentration of the drug is not attained until after the third week, it seems highly advisable to institute the suppressive treatment at least two weeks in advance of exposure so that at the time when clinical symptoms may be expected to appear a high plasma level will have been achieved. Sometimes, however, the necessity to travel to the malarious region by boat causes postponement of the beginning of the treatment since the taking of atabrine may very considerably aggravate seasickness. If an individual has taken atabrine faithfully six days of every week all the while he has remained in a malarious zone and then stops taking it when he leaves the zone he may expect to come down with his first clinical attack within two or three weeks; since this is not true causal prophylaxis the patient is simply obliged to recognize the fact that he will have malaria when he stops taking the drug, but the point of practical importance is that he should continue taking the drug after leaving the malarious zone until he reaches a region in which prompt hospitalization and expert medical care can be had.

In some medical commands during the war, atabrine was used in a larger suppressive dosage than the 0.6 Gm. obtained weekly by the daily ingestion of a 0.1 Gm. tablet; *i.e.*, the drug was taken twice weekly in a dose of 7½ grains (0.5 Gm.), giving a total dosage for the week of 1.0 Gm. No statistical comparisons of the larger and smaller suppressive dosages have been seen by me as yet, but I have been privately informed by a number of furloughed medical officers, and McCorkle (1944) has stated in the literature, that the higher dosage was much more effective and no more toxic than the smaller dosage.

Quinine.—When atabrine is not available or if the patient cannot take it then quinine must be substituted for suppressive treatment. The dosage recommended in the Surgeon General's letter is 10 grains (0.6 Gm.) of quinine sulfate taken daily at the evening meal. The taking of this dosage over a considerable period of time is frequently attended by symptoms of cinchonism.

Danger of Suppressive Treatment.—How much permanent damage has been done through the years by quinine prophylaxis is unknown to me but

surely the amount cannot be very great else one would read or hear of or see cases at intervals; that malaria itself causes neurological sequelae must not be overlooked in assessing damage allegedly due to the drug. Of permanent residuals of atabrine ingestion there seem to have been none recorded as yet; Junge (1939) reported 20 Europeans in Liberia who were said to have taken the drug continuously for seven years without harm save, of course, a constantly stained skin. Findlay and Stevenson (1944) concluded from their study of a large number of patients on the West Coast of Africa that no increased degree of resistance to atabrine therapy is exhibited by patients taking atabrine as a suppressant.

MEASLES AND GERMAN MEASLES

(*Rubeola, Morbilli; Rubella, Rötheln*)

Measles is an acute infectious disease of whose victims more than 95 per cent are under fifteen and more than 50 per cent under five years of age. Stillerman and Thalhimer (1944) established the attack rate of measles in an urban community at about 75 per cent for all ages, rising to 85 to 90 per cent for children between one and ten years of age, and dropping sharply after 10 to between 15 and 40 per cent. Infants under six months of age are usually immune, but they may actually be born with the disease if the mother is ill of it at the time of her labor. Adults also are susceptible, as was distressingly shown during War I when severe epidemics prevailed in the American mobilization camps among recruits from rural districts who had not been immunized through having an attack in their childhood. Up to the time of writing, measles had not presented a major problem in the armed forces during War II. In ordinary times the disease is endemic among children in large cities and often becomes epidemic in the winter months. In New York City in recent even-numbered years the cases have averaged about 35,000, while in the odd-numbered years there have been only about 3000 cases. During War II the regular biannual cycle of epidemics was broken in London, probably as the result of the closing of schools and the evacuation of large numbers of children, and in Manchester and Birmingham the epidemics were reported as having been delayed and mild.

The early symptoms of measles are catarrhal inflammation of the eyes, nose and upper respiratory tract, fever, and the malaise, chilliness, loss of appetite, vomiting, and so on, which characterize many of the acute infectious diseases in their incipiency. Then, on about the fourth day and often after the fever has entirely disappeared, the typical dusky, crescentic, blotchy, maculopapular rash appears, principally on the face and back, and is accompanied by a recrudescence of all the symptoms. Early in the attack there is frequently a reduction in the number of circulating lymphocytes, a helpful diagnostic sign; Koplik's spots (an eruption on the buccal mucous membrane) often appear too late to assist toward an early diagnosis. After the eruption reaches its height, which occurs in from thirty-six hours to three days, the patient begins rapidly to improve, though the skin usually retains for a week or more a brownish stain where the eruption has faded. The branny desquamation is complete within ten days.

In Stillerman and Thalhimer's (1944) study of 266 intimately exposed sus-

ceptible family contacts one month to fourteen years of age, the incubation period was ten to fourteen days for 80 per cent of the contacts, fifteen to nineteen days for 14 per cent, and less than ten days for 6 per cent. The proportion of patients with an incubation period of fifteen days or more was significantly greater in the twelve- to twenty-three-month age group.

Measles respects neither climate nor race, but it was apparently not differentiated by the classical ancients. The first clear description is that of Rhazes (860–932 A.D.), during the period of the Mohammedan ascendancy in medicine. In later times it was confused with scarlet fever, but Sydenham clearly differentiated the two diseases in the seventeenth century. Caulfield (1943) showed that the diagnostic importance of Koplik's spots was recognized by Hazeltine in the United States in 1802, almost a century before Koplik's description. Due to its many complications—of which bronchopneumonia, laryngitis with edema, and enteritis are the most serious—measles mortality was formerly very high (6 per cent in good hygienic and nutritional surroundings, 15 per cent in institutions, as high as 35 per cent in barrack epidemics), but in recent years the death rate has been steadily declining. Complicating encephalitis and other clinical types of nervous sequelae do not very much increase the total mortality because the cases, though often fatal, are rare, though the incidence has seemed to be increasing in recent years. Perhaps there is some relationship between measles and appendicitis (Hudson and Krakower, 1936); at any rate when the latter is diagnosed, operation is apparently indicated though measles is present. Cases with a bullous or pemphigoid tendency, and also instances of noma or cancrum oris as a complication, are fortunately extremely rare.

Claims have been made by several workers that they have identified the causative organism in the form of a visible coccus, but generally satisfactory substantiation is lacking. Inclusion bodies have been found in smears from the nose and from Koplik's spots, and it is the consensus among bacteriologists that the etiologic agent is a filtrable virus. The frequent finding of certain giant cells in the lymphatic tissues during the prodromal stages is still without explanation. The possibility of a second attack of measles is admitted but such an occurrence is certainly one of the greatest of medical rarities. Wells' (1944) study of the seasonal patterns of spread of measles seemed to support the theory of air-borne droplet transmission of the disease.

German Measles (Rubella, Rötheln).—This highly contagious disease resembles measles and scarlet fever but is distinct from both. It, too, is probably caused by a filtrable virus present in the nasal secretions. The differential points in its diagnosis will not be gone into here; suffice it to say that an outstanding feature of the disease is an adenitis of the mastoid, occipital, cervical, and often the inguinal and axillary glands. An attack of measles seems to predispose to infection with German measles. Complications are rare and usually not severe. In Pickles' (1942) cases in which he could be positive of the only possible exposure, the incubation periods ranged between fourteen and seventeen days. During an epidemic of unusual severity in Australia in 1940, abnormalities including cataracts, deaf-mutism, heart disease, microcephaly and mental retardation were observed in distressingly many instances in infants born to mothers who had suffered from German measles during their pregnancy; indeed the data gathered by Swan *et al.* (1943) suggested that the chances of giving birth to a congenitally defective child when a woman contracts rubella within the first two months of pregnancy are almost 100 per

cent and that if she contracts the disease in the third month they are about 50 per cent. More recently, Reese (1944) reported three similar instances of congenital defects in New York City and Erickson (1944) eleven such cases from California. It has been suggested that perhaps the virus, which was probably altered in Australia during the period when large numbers of susceptible recruits were herded together in military camps there, has gained access to the United States.

THERAPY

General and Nursing Care.—The general treatment of measles is that of grippe. Especial care *must* be taken to prevent cross infection, as death rides jauntily in the wake of complications here. Complete isolation with the nurse is the ideal to be approximated as closely as possible. Keep the patient warm in an airy room, protected from direct drafts. Admit all the sunlight possible, but protect the eyes, by the use of either dark glasses or improvised screens, and irrigate them frequently with boric acid solution; the application of petroleum jelly may prevent adhesions of the lids. Placing the child for a few minutes in a warm pack will often "bring out" a delayed rash. The irritation of the skin which is sometimes annoying during the period of the rash will usually yield to sponging with a dilute sodium bicarbonate solution; if excessive, 1 per cent phenol may be substituted. The daily bath should be continued during the desquamation period, but it is well to follow it at this time with an application of petrolatum. Petrolatum to soften crusts, and sprays (see Common Cold) for whatever they may be worth, are available for keeping the nose clean and comfortable, but their application in a way that will suit the young patient will tax the ingenuity of any nurse.

Watch the ears, watch the throat, watch the temperature and respirations: in a word, *watch for complications.*

Sulfonamides.—Despite the fact that these drugs have of course had considerable trial in measles, the most extensive study which has come to my attention, that of Gibel and Litvak (1942), in which there were 200 sulfathiazole treated cases and 201 untreated controls, showed that this drug used routinely did not reduce the length of the primary pyrexia caused by measles, did not prevent the development of secondary complications, did not reduce the duration of such complications with the exception of bronchopneumonia and did not reduce the period of hospitalization.

Amidopyrine.—Experience through the years has not sustained early claims made for this drug and there is therefore no reason to retain in the book a description of its method of employment.

Convalescent Serum.—Kohn *et al.* (1941) felt that the intravenous administration of 40 to 50 cc. of serum is indicated in debilitated children, in those recovering from whooping cough and other infectious diseases, and in children in whom measles developed during the course of another acute or chronic disease. They treated 29 children in the pre-eruptive stage, *i.e.*, after fever and Koplik spots were present but before the rash had appeared, and thought that definite modification was obtained in 23 of them. Thalhimer said that he had received many reports of the satisfactory use of 10 to 20 cc. intramuscularly, but at the time of his report (1939) was still skeptical of the value of this practice.

Gamma Globulin.—This agent, discussed more fully under Prophylaxis later, was used in the treatment of measles in its early stages by Stokes *et al.* (1944). Of 31 individuals injected in the pre-eruptive stage (see above), there

appeared to be modification of the disease in 24; of 30 individuals injected after the rash had started, there appeared to be modification of the disease in 13.

PROPHYLAXIS, *i.e.*, PREVENTION AND MODIFICATION

Measles spreads so rapidly because it is most infectious in the period prior to the appearance of the eruption. After the eruption has reached its height the contagiousness is practically nil; indeed, many municipal health departments permit the release of a child from quarantine five days after this time; provided, of course, that it is well and that the acute rash has disappeared. The bounden duty of physicians toward the individual and the community is to quarantine all susceptible exposed persons for a period of two weeks from the date of exposure; this is the practice of most departments of health, but Hobson (1938), in England, maintained that three weeks would be a safer period since he had seen first prodromal symptoms on the fifteenth day after exposure and no rash until five days later.

Available Prophylactic Agents.—The interested reader must consult an earlier edition of the book for a description of the employment of adult whole blood and fresh parenteral serum, for these methods have not caught on sufficiently to warrant the continued allotment of space to their discussion; in what follows therefore only those agents are included which are in considerable use.

Stored Convalescent Serum.—The serum of the patient convalescing from measles may be safely collected five days after defervescence. At the Milwaukee Serum Center (Hardgrove, 1941) it is obtained preferably from the end of the second week to the end of the second month, but neither the Council on Pharmacy and Chemistry (1944) nor the U.S.P. XII places a limit upon the date of collection. The principal sources from which this serum may now be obtained are the Milwaukee Serum Center, Samuel Deutsch Convalescent Serum Center of Michael Reese Hospital in Chicago, Children's Hospital Convalescent Serum Center in Los Angeles, and the Serum Exchange of the Children's Hospital in Philadelphia. The potencies of various batches of serum probably vary widely at present and will continue to do so until some method of titrating and standardizing is developed. Nor do we know precisely the rate of deterioration; at the Milwaukee Serum Center it is felt that dosage had better be increased if the serum has been in storage more than a year.

Stored Adult Serum.—The pooled serum of adults or of older children is used because of the difficulty of obtaining sufficient serum of recent convalescents. Burnet (1935) showed that the serum of adults up to fifty years of age is just as potent as that of younger persons, but that all such serums lose about 40 per cent of their value upon six months' storage though retaining this lowered value for about another eighteen months. Experience has shown that repeated and direct exposure makes for high potency even without the history of an attack of measles; doctors and nurses actively engaged in work in infectious disease wards make good donors, for example.

Lyophilized Adult Serum.—A considerable advance was made by Lichtenstein (1931) and McGuinness *et al.* (1937–1943) by the use of serum dried in vacuum from the frozen state, the advantage of such serum being that it may be reconstituted and injected in much smaller volume than that of the original serum from which it was obtained.

Placental Extract.—The use of the globulin "extract" obtained from pooled placental sera was popularized largely as a result of the efforts of McKhann and his associates in the period between 1933 and 1937. So long as nature con-

tinues to take its course there will always be a supply of placentas from which to obtain immune globulin and therefore this agent is available to all physicians through the pharmaceutical houses. But, as in the case of convalescent serum, we have as yet no means of standardizing this preparation.

Human Serum Gamma Globulin.—In recent times the Fraction II of a serum gamma globulin concentrate derived from pooled normal human plasma by the methods of Cohn *et al.* (1944) has been introduced into the prophylaxis of measles. This new agent, obtained from plasma from the blood collected by the Red Cross for the armed services, was originally available only to the Army but has now been made available to civilian physicians also. The new gamma globulin is really a by-product in the processing of serum albumin from the pooled plasma.

Choice of Agent.—Stored adult serum does not cause reaction but it is not much employed because of the relatively high dosage in which it must be given. Reconstituted lyophile adult serum may be given in somewhat less than half the quantity, but not a great deal of experience has been had with this agent as yet. The new gamma globulin has the two advantages of being given in very small dosage and not causing reaction, and the results reported with it to date, those of Ordman *et al.* (1944), Stokes *et al.* (1944), and Greenberg *et al.* (1944) indicated that its protective value is at least as high as that of any of the other agents. In the study of Greenberg *et al.*, gamma globulin was administered to 814 household contacts, none developing regular measles, 78.7 per cent being completely protected and 21.3 per cent having modified measles; among the cases of modified measles 92 per cent were mild and the remaining 8 per cent only moderate in severity. Most experience so far has been with convalescent serum and placental extract, the former not causing reactions but being expensive and not everywhere available, the latter everywhere available but quite prone to cause reactions (McKhann admitted either local or systemic, or both, reactions of moderately severe degree in about 8 per cent of cases given placental extract). Regarding the efficacy of these two agents the most satisfactory study that I have seen reported is the one made by four board of health officers in Chicago and reported by Bundesen *et al.* (1940). All the children, comprising a total of 1305, were seen in their own homes and were considered to have been thoroughly exposed because in each instance the physician visited the home only when measles was reported to be present in one of the children, and all the homes were of the poorer overcrowded sort in which few children escape the disease. Wherever possible the younger children were inoculated and the older susceptibles (*i.e.*, with no history of having had measles) used as controls, but this was fair since the age distribution of the controls showed that there were plenty of very young children among them: under one year, 14; one to three years, 115; four to nine years, 186; ten years and over, 13. Altogether, 678 received placental extract, 299 convalescent serum and 328 were held as unprotected controls. In the placental extract group, 52.1 per cent failed to contract the disease and the total of those protected (*i.e.*, no attack or a modified attack only) was 95.2 per cent. In the serum group, 73.2 per cent did not contract the disease and the total proportion protected was 97.9 per cent. In the control group, 26.6 per cent did not contract the disease; but in this group many who came down with it had only a mild attack, so that "protection" here (in the sense of no attack or a mild attack) was 82.9 per cent. Therefore, one may say that serum was slightly superior to placental extract, and both were vastly

superior to no treatment at all, in the matter of completely preventing the occurrence of the disease; and that from the standpoint of "protection" as the term is used above there was an advantage of 12 to 15 per cent in using one or the other of the agents. In addition, the following facts regarding severity of the disease must be carefully weighed: of those given placental extract and later contracting measles, 78.9 per cent were prostrated; of those coming down after serum, 73.7 per cent were prostrated; of those attacked without any protection, 97.4 per cent were prostrated.

Timing the Injections.—It is usually stated that if these agents are given from the first to the fourth or fifth day after exposure complete protection is afforded and that if they are given from the fifth or sixth to the ninth day only attenuation of the attack will be accomplished. But since the disease is considered to be contagious as soon as the early catarrhal symptoms appear it is very difficult to know just how long the exposure has been (one very rough rule is that the contact will have been exposed four days when the rash appears on the sick child). In the study of Bundesen *et al.*, above cited, there was very little variation in the results where the injections were given before or shortly after the fifth or sixth days, but in the study of Top and Badger (1941), in Detroit, in which convalescent serum was given to 1133 contacts exposed in homes, there was an appreciable advantage (from the standpoint of avoiding the disease altogether) in giving the injection during the first three days and somewhat less up to and including the sixth day, the most noticeable effect being in the group under one year of age. In the large-scale study of Stillerman *et al.* in New York, there was no significant difference from the standpoint of complete protection between the fourth and seventh day after exposure, but on the eighth day after exposure, even though the serum had a definite modifying effect, it did not prevent measles. Using gamma globulin, Greenberg *et al.* found that the amount of complete protection was not affected by the day of exposure on which the injection was made from the third to the eighth day following initial exposure to the original case.

Dosage.—Pooled adult serum is given in dosage of 10 to 80 cc. McGuinness *et al.* (1943) stated that the powdered residue from each 10 cc. of lyophile adult serum may be redissolved in 4 cc. of sterile distilled water for intramuscular injection, and that for intravenous injection the serum may be restored to its original volume if so desired. Placental extract is usually given in dosage of 2 to 4 cc. but dosage up to 10 cc. has been employed by Hobson (1938) and others. Stillerman *et al.* (1944) stated that for complete protection with convalescent serum the optimum dose after an exposure of four to seven days is 10 cc. for contacts six to eleven months of age, 15 cc. for those twelve to twenty-three months of age, and 20 cc. for those two to three years of age; if modified measles is desired, 5 cc. was held to be sufficient between the fourth and eighth day after exposure for contacts up to twenty-four months of age and 10 cc. for those older. Stokes *et al.* (1944) stated the following dosage of the new gamma globulin: for attenuation in children five years and under, 0.25 to 0.5 cc., and for full protection in that group 2.0 to 2.5 cc.; for attenuation in children six to twelve years, 1 to 1.5 cc., and for full protection in that group 4 to 5 cc.

Prevention or Attenuation.—Stokes *et al.* (1944) stated that though one can achieve either full protection or only attenuation within a specified range of dosage with considerable accuracy for a group of children, the physician cannot as yet tell the parents of the exposed susceptible whether or not their child will be completely protected because there is apparently a notable difference

in susceptibility in individual children. Should one in the case of most contacts attempt to prevent the occurrence of measles or merely attempt to modify its severity and lessen the likelihood of complications? I think that Schwartz (1941), of Milwaukee, expressed the consensus when he said that it often seems judicious to attempt to prevent it entirely in younger children and to modify it only in older ones. In effect such practice (*i.e.*, complete prevention) merely amounts to postponing the age at which the individual will have measles since immunity conferred by one of these agents lasts only two to six weeks. Upon the other hand the use of the preparation in such way as to permit the patient to have only a light attack of the disease apparently confers as long-lasting immunity as an unmodified attack. But since the most deadly age period by far for measles is under three years, many men make it a rule always to attempt complete protection in this group. Children of any age acutely or chronically ill with any other disease at the time of exposure to measles are also prone to have several attacks, and in them also full protection should be attempted. Finally, when measles appears in a hospital ward it is the usual custom completely to protect all children even remotely exposed, the purpose here being not only to safeguard the children but also to prevent serious disruption of the hospital service through a protracted period of quarantine. In other individuals—children or adults—not in either of the three above classes, it seems to be the consensus that the use of these preparations in such way as will permit the occurrence of a mild attack, rarely accompanied by complications but succeeded by lasting immunity, is the preferred method.

Should All Contacts Be Immunized?—In other words, is the mere fact of exposure enough to warrant an attempt being made to attenuate the expected attack if the children are beyond infancy and healthy? Perhaps in the main the answer should be "Yes" unless one is forced to use placental extract, in which case I should think that the likelihood of the contact having been really a serious one might have to be weighed in the individual case. Karelitz *et al.* (1938) showed that exposures during casual contacts at play, in busses, schools, at parties, etc., are not at all comparable to exposures in the home in their likelihood to eventuate in contraction of the disease. They said also that exposure in the home will be light if the hygienic situation is good and the patient is separated from other children of the family at once on suspicion of the disease, and also that it will be very heavy if the hygiene is poor and all the children remain together during the development of the cases. Hobson (1938), as a result of his experience in several epidemics with excellent environmental hygiene and nursing precautions in preparatory schools for boys in England, went all the way and said that healthy susceptible individuals should be permitted to experience a normal attack of measles after exposure even though convalescent serum is available; I doubt that many in the United States are in agreement with him.

MENINGOCOCCAL MENINGITIS

(*Cerebrospinal Fever, Epidemic Cerebrospinal Meningitis, Spotted Fever*)

Meningococcal meningitis is an infectious disease caused by the meningococcus (*Neisseria intracellularis*) and occurring sporadically or in epidemics with an irregular cycle. Infection probably takes place by droplet transfer from

an active case or from a healthy carrier; in War II it was amply shown that the principal factor influencing the rate of dissemination of the disease at the Army posts was the presence of a high proportion of unseasoned troops, especially, according to Sartwell and Smith (1944), when there was a rapid turnover of such troops. The predisposing influence of upper respiratory infection and of other debilitating circumstances has also been adequately demonstrated. Symptomatically, and indeed perhaps pathologically, the classical form of the disease can be divided into three stages, the first two of which are unfortunately not often recognized. The *first stage* may simply be a carrier stage without symptoms, or there may be a tonsillitis, pharyngitis, or sinusitis, or a conjunctivitis with discharge containing the causative organism. In the *second stage* the patient goes to bed, where he lies curled on his side, knees up and head bent toward them; he is extremely apathetic, loses both play of feature and modulation of voice, and when urged will complain in monosyllables of being "sore" all over his body. It is during this stage that the rash, which is usually petechial or purpuric, appears; that the organism may frequently be demonstrated in smears from the purpuric lesions has been shown by Bernhard and Jordon (1944) and others. In the *third stage* the diagnosis is most frequently made. Here there is the bursting headache, vomiting, chilliness and erratic fever, possibly delirium or coma (in children, of course, often convulsions, and in infants a gastro-intestinal disturbance or infection of the upper respiratory tract is often suggested); cloudiness of the spinal fluid with increase in pressure unless block has occurred, stiff neck and the well-known Kernig's and other signs; the organism may usually be cultivated from the spinal fluid and less frequently from the blood in this stage. Accruing experience, however, has indicated that much would be gained by regarding meningococcic disease as a bloodstream infection of which the familiar cerebrospinal meningitis is but one manifestation. Adams (1944), as a result of experience among the troops in War II, listed the following forms in which meningococcic disease may appear: (*a*) Meningococcemia with acute meningitis; this is the *third stage* of the classical syndrome described above, but every effort should be made to accomplish the diagnosis before actual signs of meningitis appear. (*b*) Acute fulminating septicemia with or without meningitis, manifested by sudden onset with marked prostration, rapidly developing profuse macular and petechial eruption, early and rapid circulatory collapse followed by death, often within a matter of hours. This is the Waterhouse-Friderichsen syndrome; as originally described, hemorrhage into both adrenal glands was found upon postmortem examination but as the cases have increased in number it has become recognized that the same course may be run without adrenal hemorrhages having occurred before death. D'Agati and Marangoni (1945) observed anuria followed by severe oliguria in their 6 cases and looked upon this failure of renal function as an evidence of the destruction of adrenal cortical tissue. Occasionally patients with this syndrome will collapse and be dead within a few hours without having experienced any premonitory period of feeling ill; another peculiar characteristic is the rapidity with which the eruption develops, it being sometimes possible to see the spots appear as one looks at the patient. From the standpoint of a medical examiner, Martland (1944) made the point that death occurred so rapidly in this syndrome as sometimes to require differentiation in civilian life from food or chemical poisoning, trauma, negligence and even homicide. (*c*) A less severe form of bacteremia characterized by inflammation of one or more joints, a less intense eruption, often macular

rather than petechial, and aching in the muscles of the extremities; parenthetically one should perhaps remark that Fox and Gilbert (1944) have not found that cases with joint involvement are invariably otherwise mild. (*d*) A chronic form of bacteremia, in which bouts of fever, accompanied by joint pains and mild eruption, occur at intervals of weeks or months with intervening periods of relatively good health.

The highest incidence of the meningococcal infections is in children under ten, then in adolescents and then in young adults. Late winter and spring usually marks the peak of the seasonal increase in cases. Mortality varies greatly from year to year but prior to the use of sulfonamides in therapy it was always high—30 to 90 per cent or even higher.

So far as I am aware the first published accounts of meningococcal meningitis were those of Gaspard Vieusseaux (1805) at Geneva, and L. Danielson and E. Mann (1806) in Massachusetts. In 1811, the American, Elisha North, published a large monograph on the subject. Weichselbaum discovered the causative organism in 1887, and Flexner introduced the antiserum in 1909.

THERAPY

Sulfonamides.—The use of these drugs has completely altered the outlook in the meningococcal infections in recent years. In the United States during 1943 we had the most extensive outbreak in our history but the mortality in soldiers training in the country at the time was held down below 4 per cent, which is to be compared with the mortality of 39 per cent in War I soldiers. When the drugs of this group are promptly and properly employed there is usually a return of the temperature to normal and practically complete disappearance of the other acute symptoms within two to six days—first signs of improvement are often seen within a few hours of beginning the medication. Delirium subsides or the eye of the comatose and apparently moribund patient loses its glaze, infants begin to feed again, the cerebrospinal fluid tends rapidly toward the normal (often becoming sterile within twenty-four hours), and so on. The incidence of complications and residual symptoms is also astonishingly reduced.

Sulfadiazine has proved more effective than the earlier sulfonamides in these infections, but the studies of Lepper *et al.* (1943) and Goldring *et al.* (1945) indicated that the newer drugs, sulfamerazine and sulfapyrazine, are probably just as good.

Methods.—Discussing their ample experience at Bellevue Hospital, Appelbaum and Nelson (1944) said that they employed the following scheme of sulfadiazine dosage: on the first day of treatment, children under one year of age received from 2 to 3 Gm.; children from one to three years of age received from 3 to 4 Gm.; children above that age received from 4 to 7 Gm.; and adults from 9 to 12 Gm. One quarter to one third of this amount was given as the initial dose and the remainder divided and administered at intervals of four hours. In slightly more than half of their cases the drug was given by vein during the first twelve to twenty-four hours, usually in a 5 per cent solution in distilled water; in very severe cases the parenteral medication was continued for a longer period of time. It was the belief of these observers that the parenteral route should be employed only in severe cases and in those patients who are unable to take or retain oral medication, but the testimony of numerous physicians in the Army in War II supported the statement of Adams (1944) that the first dose should routinely be given intravenously for the reason that the patient's condition can change so rapidly that there is no justification,

once the diagnosis has been made, for losing the time it takes for an oral dose to become absorbed. Adams (1944), Thomas (1943), and others have thought it sometimes advisable in fulminating cases to give an initial dose as high as 8 Gm., but Appelbaum and Nelson (1944) believed this to be dangerous, especially if the drug is given by vein. There is no indication for the administration of the drug intrathecally as the drug given orally or intravenously will reach a concentration in the cerebrospinal fluid of two thirds to four fifths of that found in the blood. Just what this blood level should be cannot be dogmatically stated, but it seems to be the consensus that 10 to 15 mg. per cent should be striven for; indeed Thomas (1943) said that he did not consider it harmful to attempt to maintain a level of between 15 and 25 mg. per cent provided the likelihood of hematuria is reduced to a minimum by forcing fluids and giving alkalis, while Goldring *et al.* (1945), with the same qualification, attempted to maintain a level of 20 to 40 mg. per cent. The question then of fluids and alkalis arises. It is agreed that any patient receiving the sulfonamides should be given enough fluid to insure a twenty-four-hour urinary output of at least 1500 cc. but it is said that the fever and sweating of these patients often quickly dehydrates them to such extent that an intake of 4000 cc. or more may be necessary in order to maintain a 1500 cc. output; furthermore, since precipitation of the acetylated sulfonamide is much reduced in an alkaline urine it is of advantage from the beginning to take steps to reduce urinary acidity. The frequent practice is of course to "push" fluids and give sodium bicarbonate gram for gram with the sulfadiazine, but at one of the Army posts, Ochs and Peters (1943) routinized the matter very satisfactorily in the treatment of desperately ill patients as follows: preparatory hydration and alkalinization of the patients was carried out by the giving of 2000 cc. of $\frac{1}{6}$ molar solution of sodium lactate intravenously before giving the sulfonamide. The first dose of sodium sulfadiazine was then given as a 5 per cent solution in 200 cc. of sterile distilled water. After the sodium sulfadiazine was given, 1000 cc. of 5 per cent dextrose in saline solution and 1000 cc. of 5 per cent dextrose in sterile water were administered, the patient thus receiving a total of 4000 cc. of fluid in twenty-four hours. The daily fluid balance and alkalinization were carried out as indicated until nausea and vomiting ceased and the patient could take oral medication. No further alkali was given after the first three days and in spite of the cessation of alkaline therapy no renal complications occurred.

There does not seem to be complete agreement on the necessary duration of chemotherapy in these cases. Appelbaum and Nelson (1944) stated that in the beginning of their study they continued to give sulfadiazine for four or five days after the temperature became normal but that more recently they found that they could safely discontinue chemotherapy after the patient had been afebrile for twenty-four to forty-eight hours and had received a total of 15 to 20 Gm. of the drug. Regarding the value of spinal fluid examination, these observers stated their belief that undue stress is often laid on the importance of the total cell count, for they often discontinued chemotherapy in the presence of a considerable pleocytosis; a rise in the sugar content of the fluid and a disappearance of the organisms were looked upon by them as the more important determinants, though control of the infection was not infrequently obtained before the return of the sugar to normal. It would therefore seem that reliance on symptomatic improvement may be considered a safe guide to the termination of sulfonamide administration in the meningococcic infections.

Toxicity.—See the chapter on Sulfonamide Toxicity at the end of the book.

Penicillin.—The largest scale study of the use of this agent in meningococcal meningitis which has come to my attention is that of Rosenberg and Arling (1944), who treated 76 patients; 75 of the 76 patients recovered, the one fatality occurring in a patient admitted in a moribund state. Ten thousand Oxford units of sodium penicillin, dissolved in 10 cc. of physiologic saline solution, were slowly introduced into the subarachnoid space after the usual type of diagnostic lumbar puncture and spinal canal drainage (the paramount importance of draining the spinal canal as completely as is feasible before injecting the penicillin was stressed). The intrathecal administration of the agent was repeated at twenty-four-hour intervals until clinical improvement, sustained fall in temperature, or a decrease in the meningeal signs was manifest and until the stained smears and cultures of the spinal fluid revealed no organisms. As penicillin was injected intrathecally with each lumbar puncture without awaiting the results of the bacteriologic studies, this plan in effect was tantamount to administering an additional dose of penicillin after the spinal fluid became sterile. Rosenberg and Arling felt that in some instances it was unsafe to withhold treatment pending the results of the spinal fluid cultures. The persistence of coma was regarded as an indication for further intrathecal therapy, and in the most severe infections and in those in which coma lasted forty-eight hours or longer, intrathecal penicillin was continued until the spinal fluid was bacteria-free on three successive days. Penicillin was also administered either by the continuous intravenous drip method at the rate of 5000 units per hour or intramuscularly in doses of 15,000 units every three hours, the dose being reduced to 10,000 units every three hours if improvement was satisfactory. Generally, penicillin was given intravenously (40 units per cubic centimeter in a 5 per cent dextrose solution) for the first eight hours and continued intramuscularly thereafter. Patients with the fulminating types of infection received penicillin intravenously at the rate of 10,000 units per hour for four hours initially. Most of the patients recovered following only one or two intrathecal injections but some required as much as four to six. Intravenous and intramuscular penicillin did not prove effective in the treatment of such complications of meningococcemia as acute arthritis, epididymitis, orchitis, or pericarditis.

Serum and Antitoxin.—The chemotherapeutic agents have now practically completely superseded serum and antitoxin. Reimann (1944), reviewing the matter for the Council on Pharmacy and Chemistry, stated that for the few patients who are sensitive to sulfonamides and for the still rarer instances of infection with sulfonamide-resistant meningococci, the available potent type-specific horse antimeningococcic serum alone should be used intravenously, but never intrathecally, in adequate dosage with promptness and precision. The intravenous dosage employed by Gregory *et al.* (1940) was 30 to 60 cc. for infants and young children, 90 to 120 cc. for older children and adults, the serum being diluted two or three times with physiologic saline solution containing 5 or 10 per cent dextrose; Hoyne (1940) used larger dosage, 150 to 300 cc. A rabbit serum is now having experimental trial but is not yet available for clinical use. Hoyne (1940) used 180 to 300 cc. doses of antitoxin, but Reimann (1944) felt that there was no firm evidence in support of the use of this agent at all; he further felt that there is no evidence to prove that combined chemoserotherapy is superior to chemotherapy alone. The Council voted to drop both the serum and the antitoxin from New and Nonofficial Remedies.

Spinal Drainage.—Frequent drainage of the spinal canal, without other treatment, was the sheet anchor of therapy prior to the development of specific measures, and there are those who still champion it as adjuvant to other treatment; Thompson (1937), just before use of the sulfonamides began, even advocated a complicated type of continuous drainage. Bryant and Fairman (1939) said that the primitive natives whom they treated successfully with sulfonamides themselves noted the superior improvement in those who had also been tapped and soon demanded puncture in all cases. Puncture was rather generally employed to relieve symptoms of intracranial pressure during the epidemic in the American Army in War II. Ochs and Peters (1943) said that repeated punctures, made hourly in some cases, were necessary to relieve the embarrassed breathing and to prevent death from respiratory failure; eight of their patients had three or more punctures to relieve intracranial pressure. They emphasized, however, that the most frequent cause of restlessness in their semi-comatose and comatose patients was a distended bladder and that they never considered restlessness alone as due to increased intracranial pressure until catheterization had been done. In spite of the testimony in favor of spinal puncture, I think the reader will do well to heed Hoyne's advice of several years ago to avoid puncture if at all possible because frequent drainage is more apt to promote hydrocephalus than to prevent it; his opinion, based on a very large experience, was that "the fewer the punctures the fewer the hospital days."

Opiates.—Morphine or dilaudid is usually given without stint to control violent symptoms during the first twenty-four to forty-eight hours, though some observers believe they raise intracranial pressure and counsel against their use; Hoyne described the treatment of 134 patients, none of whom had been given any opiates.

Special Measures in Waterhouse-Friderichsen.—In these cases it has latterly become customary to employ plasma to combat the shock-like state, and to attempt to overcome the effects of possible adrenal insufficiency by the injection of adrenal cortex extract, desoxycorticosterone and epinephrine (see Index for methods of using all of these agents). Bush and Bailey (1944) stated that it was only in this syndrome that they continued to use antitoxin; they had no way of knowing whether it was helpful or not but they gave it to all of their six patients, two of whom recovered.

PROPHYLAXIS

General Measures.—When meningitis is epidemic the customarily employed control measures consist in isolation of the patient and an attempt to protect the general populace by measures designed to prevent overcrowding, fatigue and exposure. Prompt hospitalization or isolation of all cases of common respiratory illnesses during an epidemic period would also probably be ideally desirable but its practical accomplishment is utterly impossible. As a matter of fact, if a health officer were given carte blanche to rule a population at will in an area in which the disease was epidemic today it is doubtful if he would really know what measures to institute, for it is usually extremely difficult to trace direct contact between clinical cases. It would seem that a virulent strain passes from one healthy carrier to another through many hosts before it reaches an individual in whom invasion is successful; Mueller (1943) pointed out that when such invasion does occur all trace of the intervening chain of passages has been lost.

Sulfonamide Prophylaxis in Closed Groups.—The knowledge has been at hand for some time that the sulfonamides in moderate dosage are effective in ridding carriers of meningococci, but practical application has lagged for the reason that it would be useless to attempt detection and sterilization of the carriers in an open and fluctuating population. However, War II presented the ideal conditions for a trial of sulfonamide prophylaxis in closed controlled populations. A number of such trials were made during the epidemic of 1943 in the United States and all were eminently successful. The study which employed the largest numbers, that reported by Kuhns *et al.* (1943), will be summarized here. These observers gave prophylactic sulfadiazine to more than 15,000 soldiers at two Army camps when the disease was very prevalent during the spring of 1943, 18,800 soldiers in the same camps serving as untreated controls. The method employed varied only as to dosage of sulfadiazine in the two camps. In one camp the dosage was 1 Gm. by mouth three times daily for three days; in the other camp the dose was 1 Gm. twice daily by mouth for two days. In the first camp the carrier rate among the troops to be treated was 36 per cent and in the control group 38 per cent. During the eight-week period of observation subsequent to the completion of prophylactic therapy no cases of meningococcic meningitis developed among the 8000 treated men while at the same time 23 cases occurred among the 9300 untreated controls. During this period the carrier rate in the treated group went down to as low as 2 per cent and was never above 7.2 per cent whereas in the untreated group it never went lower than 30 per cent and rose as high as 57.2 per cent. The results were entirely comparable in the second camp in which the treated group was approximately 7000 and the untreated controls 9500, the carrier rate being 30 and 29 per cent respectively before the beginning of the experiment and the lows after the experiment being 0 and 29 per cent; 17 cases of meningitis occurred in the untreated group and 2 cases in the treated group; one of these two men, however, was probably infected elsewhere because he did not come down with meningitis until five weeks after he had been transferred to another organization.

From the study above summarized it may be concluded that a dose of 2 Gm. of sulfadiazine daily for two days was highly effective in preventing the spread of meningococcic meningitis. Phair *et al.* (1944), and Pilot (1945), indeed showed that a single 2 Gm. dose may be amazingly effective in lowering the carrier rate, and the former observer also found that sulfamerazine was apparently equally as effective as sulfadiazine but no more so. However, it cannot be too strongly emphasized that Kuhns and his associates were convinced that the effectiveness of their prophylactic experiment depended upon: (*a*) treating all individuals in the group simultaneously; (*b*) treating all personnel who joined the group subsequent to the institution of prophylaxis before they were incorporated into the group; and (*c*) keeping the treated group closed to reinfection from outside sources. The reader will be aware at once of course of the impossibility of applying such measures in ordinary civilian practice. As a matter of fact, even if it were possible to do so there is some reason to doubt the advisability of such a step for the reason that until more exact knowledge regarding sulfonamide sensitivity has been gained we must look upon the large scale employment of these drugs in small dosage under ordinary civilian conditions as an unwarrantable step not to be endorsed by the medical profession.

MILIARY FEVER

This is a disease of unknown etiology that occurs in limited epidemics of not more than a week or two. There is high fever, great sweating, profound prostration and an erythematous rash with miliary vesicles. Between 1718 (when it was first described, though it had probably existed before) and 1861 there were about 175 epidemics recorded in France alone; Italy and southern Germany have also known the disease, but not, I believe, Great Britain. The last reported outbreak occurred in France, in 1926. The mortality is usually low.

It is very doubtful if this disease is the same as that "sweating sickness" which devastated England and the Continent several times in the fifteenth and sixteenth centuries, for John Kaye, or Caius, an eminent London physician who described the outbreaks of 1552, had nothing to say about an eruption of any sort.

THERAPY

I do not know of any treatment that warrants particular description.

MUMPS

(*Epidemic Parotitis*)

Mumps is an acute infectious disease probably confined to man, though allegations are sometimes made that it is seen also in goats, dogs and cats. It occurs all over the world and tends to become epidemic during the winter and spring months, but is much less contagious than measles, chickenpox and whooping cough. The greatest age frequency is between five and fifteen years, but the disease also often occurs among young men crowded together, as in barracks or ships or prisons, and among student nurses in hospitals. In the United States Army during War I, mumps stood third on the list of important diseases from the standpoint of noneffectiveness, ranking in this respect next to venereal disease and influenza, but Simmons (1943) stated that in War II the overall incidence of mumps was low, this latter fact probably being due, as pointed out by McGuinness and Gall (1944), to the fact that in the years between the two wars there occurred a great decrease in isolation in rural areas where many persons formerly reached adult life without exposure to the usual communicable diseases. Attacks in early infancy and in the years beyond forty are rare but not unknown. Unusual but well-authenticated second, third and even fourth attacks are on record. A case has been recorded complicating pregnancy in which the symptoms were so severe as to jeopardize the patient's life.

The chief symptom of mumps is a swelling of one of the parotid glands, accompanied by stiffness of the jaws and pain which is accentuated upon opening the mouth or attempting to swallow. There is usually a slight rise in temperature. In most cases the opposite parotid swells also but involvement of the other salivary glands is relatively infrequent. Only in the more severe cases do the constitutional symptoms progress beyond slight prodromata, such as headache, chilliness and loss of appetite. A slowed pulse rate and leukopenia with relative lymphocytosis are observable in practically all cases. Greene and

Heeren (1937) said that the spleen often becomes palpable. Murphy *et al.* (1943) found blood diastase activity increased in mumps and Applebaum (1944) observed an elevation of serum amylase in a great majority of cases; a complement fixation test is being evolved. The attack is usually terminated within a week of its inception. A quarantine period of two or even three weeks is often enforced, but since experience indicates that communicability very rarely extends beyond the duration of the swelling, Gordon and Heeren (1940) considered the following regulations satisfactory: (*a*) Keep children exposed at home away from school for three days to see whether they too are affected. (*b*) Take them out of school again from the fourteenth through the eighteenth day to cover the period of incubation in them should they have become infected. (*c*) Isolate the sick child unitl the swelling of the gland has subsided, or at least seven days.

Orchitis, which occurred most commonly about the sixth day of illness in Worden's (1944) series of 250 cases of epidemic mumps, is said ordinarily to have an incidence of only 18 per cent in boys past puberty and young men who are attacked by the disease, but in War II, Dermon and Le Hew (1944) reported an incidence of 35 per cent in 129 cases in a small task force, and a special commission of the United States Army Medical Department stated (Bulletin of the U. S. Army Medical Department, 79, 10, 1944) that in the moderate epidemics of mumps occurring in the South the incidence of orchitis approximated 30 per cent. Orchitis is frequently preceded by epididymitis, is accompanied by fever and a considerable degree of prostration and results in atrophy of the testis in about half the cases if untreated. It does not seem that anyone has followed a series of cases to determine how many of these individuals become sterile but the occurrence is believed to be rare. Loss of secondary sexual characteristics, libido, or the ability to perform the sexual act is extremely rare. Gilbert (1944) concluded from an extensive survey that there is no direct relationship between mumps orchitis and later tumor development. The exact incidence of oophoritis is unknown though it is doubtful if this complication is really less common than the corresponding one in the male. In some epidemics a benign type of encephalomeningitis occurs in some of the cases; both Finkelstein (1938) and Fox (1941), the latter of Milwaukee, felt that this complication is of more frequent occurrence than generally believed, and experience in War II seems to have borne them out, for though McGuinness and Gall (1944) presented the data on only 55 cases among 1378 patients at one Army post they felt that the incidence was much higher than these figures indicated, and Candel *et al.* (1944) in a small outbreak at another post found clinical meningitis in 26 of the 38 cases, and in 79 per cent if an increased number of cells in the spinal fluid be accepted as evidence. Deafness, unassociated with meningeal involvement, occasionally occurs and is usually permanent; there are other varied and striking nervous complications but they are not often seen. Orchitis, oophoritis and meningitis have all occurred without a primary parotitis. During War II, Gellis and Peters (1944) reported the occurrence of a soft pitting edema centering over the sternum in 6 per cent of 502 patients admitted to the hospital with a diagnosis of mumps in an epidemic at a post in the South; this finding, possibly indicating a lymphatic obstruction, was also reported by Barker (1943) from a camp in Canada. In very rare instances during mumps corneal opacity and visual loss appear and disappear with marked rapidity, according to Lippmann (1943).

Wollstein was, I believe, the first to show that the virus of mumps (first

conclusively demonstrated by Johnson and Goodpasture, in 1935) is present in the mouth secretions of individuals having the disease. Droplet infection might therefore be expected to be the rule, since transmission can take place before the swelling appears; however, Habel (1945) concluded from a study of the experimental, clinical and epidemiologic evidence that under most circumstances mumps is not a true air-borne disease. We do not as yet know whether there are many, or any, individuals who are carriers of the mumps virus. Eighteen days is considered to be the usual period of incubation.

THERAPY

Very little treatment is indicated save for relief of pain by the prolonged use of hot or cold applications or of U.S.P. belladonna ointment applied over the swelling. Potter and Bronstein (1944) found that neither atropine nor belladonna given by mouth to the point of causing dilatation of the pupil or dryness of the throat was of any value. The attempt is sometimes made to have an antiseptic mouth wash used to prevent secondary infection, but this measure, if properly employed, adds greatly to the pain in most cases and is of very doubtful value. However, when the salivary ducts have become occluded by swelling and the mouth must be kept artificially moistened, there is no reason why the fluid used should not be some such antiseptic as diluted Dobell's solution.

It is generally believed that the incidence of orchitis will be greatly lessened if absolute bed rest is enjoined in boys and young men, but there are observers who doubt the possibility of statistically proving the point. The usual practice when the complication develops is to support the inflamed scrotum and make use of cold applications in a fluffy light manner so as not to increase the discomfort by their weight. A local application of 50 per cent methyl salicylate in hydrous wool fat (lanolin) is said to be serviceable. Rambar (1944) and Smith (1945) reported excellent results from the intravenous administration of plasma. A number of years ago Wesselhoeft advocated incision through the tunica vaginalis and multiple incisions of the tunica albuginea to bring about relief of pain through permitting escape of the serous fluid imprisoned under pressure, the operation taking about one minute under gas. In 1942, Wesselhoeft and Vose stated that an enlarged, hard tender testicle with chills and fever constitutes the indication for surgical interference and that while early operation relieves pain, reduces fever and avoids atrophy it is useless to operate when the process is already on the wane; they stated also that operation is not indicated in mild cases or those in which an epididymitis predominates. Both McGuinness and Gall (1944) and Finn and Palmberg (1944) found this operation of some benefit in small series of cases.

It is doubtful if the use of convalescent serum after the attack of mumps has developed alters the course of the parotitis but it is alleged to lessen the incidence of orchitis and hasten its subsidence if already established. In the reports of Teissier and of Lavergne and Florentin some years ago it was found that doses of 40 cc. are the most effective, given intravenously. Thalhimer (1939) said they had a number of recorded instances at the Serum Center in New York in which such therapy seemed helpful but felt that more experience was needed before true evaluation could be reached; the attitude of both Gordon and Heeren (1940) and Wesselhoeft and Walcott (1942) was one of skepticism.

PROPHYLAXIS

Regan, in 1925, if not the first was certainly one of the earliest users of convalescent serum intramuscularly in attempted prevention of mumps. Since that time there have been numerous reports and practically all of them favorable, but studies of series in which there were adequate controls are conspicuously missing. The reason for this is of course the fact that the serum is usually employed only when it seems imperatively necessary to prevent spread of an epidemic, as in boys' camps, wards filled with debilitated children, etc. A typical report is that of Kutscher (1940), who injected 51 susceptible boys between nine and sixteen years of age all thoroughly exposed to a case that had developed in camp, giving 8 cc. to the younger and lighter and 10 cc. to the older and heavier boys (Thalhimer recommended 20 cc. for children and 40 cc. for large adolescents and adults); 1 case developed ten days after the first but thereafter no other case during the remaining five weeks of the camping period. Lyday's (1941) experience indicated that 10 cc. of serum confers a passive immunity of probably only very short duration and that perhaps it would always be well to reinject upon subsequent exposures even if they follow the first exposure by only a few days; it is interesting that Wesselhoeft and Walcott (1942) recommended that the 10 cc. injection be repeated in three to five days.

Gordon and Heeren (1940) said that for preparation of convalescent serum, blood is preferably collected two to three weeks after the attack but that it is satisfactory in emergency to take it from persons who had their attacks many months before.

In a British Army post during War II, Beason *et al.* (1944) gave plasma prepared from measles convalescents to 470 men; it was not very evident that the protective value of the plasma was high but a very surprising fact was the development in 44.7 per cent of the inoculated men of hepatitis with symptoms not precisely those seen in ordinary infectious hepatitis.

MYCOSES

ACTINOMYCOSIS

Actinomycosis is a chronic infectious disease caused by the ray fungus (*Actinomyces bovis* being the type species), which probably exists normally among the abundant flora of the alimentary tract and gains access to the tissues through microscopic lesions, carious teeth, wounds made by penetrating foreign bodies, or reaches the respiratory tract by aspiration from the mouth and pharynx. The disease occurs quite commonly in cattle ("lumpy jaw"), sometimes in horses, hogs and sheep, and more rarely in other animals, but the fact is not yet firmly established that it can be conveyed from cattle to man, or indeed from man to man. Though looked upon as a rare disease, recent statistical studies tend to show that it occurs with much greater frequency than has heretofore been believed. Most of the cases in the United States have been seen in the upper Mississippi Valley and the northwestern states; country folk are much more often affected than city dwellers.

The essential lesions of the disease are multiple, more or less painless, abscesses, usually surrounded by a considerable area of proliferative tissue. Discharging sinuses develop from the abscesses, and the process extends by

continuity of tissue or sometimes by metastasis. Fifty per cent of reported cases have been in the region of the head and neck, usually beginning about the jaw, and here the diagnosis is not difficult. In about 20 per cent of cases some abdominal organ is primarily affected; here the diagnosis is more difficult until the lumpy process extends to the abdominal wall and a characteristic sinus appears. In approximately 15 per cent of cases the involvement is thoracic with physical signs usually indistinguishable from pulmonary tuberculosis until perforation of the external wall takes place. Rarer forms of the disease may occur anywhere in the body.

Under proper treatment the prognosis may be considered fair in the head and neck cases, very bad in pulmonary and perhaps slightly better in abdominal cases.

THERAPY

Iodides.—Sodium or potassium iodide used to be considered specific in a limited way in actinomycosis, but nowadays much doubt is felt of their real effectiveness. Certainly their use in large doses must be persisted in for a long period of time—so long indeed in many instances that one must wonder whether it was really the iodides that finally produced whatever amelioration was obtained. Fortunately, most patients tolerate the drug well. I recall a case in which I gave 640 grains (42.6 Gm.) of sodium iodide daily for a period of many months, 60 grains (4 Gm.) intravenously and the remainder by mouth. During this time the patient was delivered of a normal baby and neither the mother nor the child showed any signs of iodism. Dosage even much higher than this has been employed not infrequently.

Thymol.—Myers (1937) reported good results with thymol administered in capsules of 22 to 30 grains (1.5 to 2 Gm.) daily or on alternate days; in some instances the drug was also injected into the sinus tracts in a strength of 10 to 20 per cent in olive oil. Myers' cases were of the localized type not involving internal organs. In a small series of similar cases, Joyce (1938) also had very good success with thymol, combining its use, however, in most instances with the employment of surgery. In Clemens' (1940) case apparent recovery occurred under the drug after both a sulfonamide and deep x-ray therapy had proved ineffective. The thymol is usually given in a single dose in milk before breakfast; Clemens' patient tolerated twenty-eight days of this medication without gastro-intestinal or other disturbance. Etter and Schumacher (1939) reported the progressive improvement and apparently complete recovery of a patient with primary pulmonary actinomycosis under thymol.

Sulfonamides.—There have been a number of reports, usually of only a single or a few cases, of the successful use of these drugs when other agents had failed. In the three cases of Dobson *et al.* (1941), one with involvement of the jaw, one of the chest and one of the abdomen, complete cure was apparently obtained. Hollenbeck and Turnoff's (1943) jaw case was apparently quickly terminated; Ladd and Bill (1943) and Pillsbury and Wassersug (1944) each recorded an apparent cure in a pulmonary case and Watkins (1944) two such cures. But there have been disappointments too; Morton (1940) failed in his 2 cases, Harris and Priestley (1944) failed in their case, and Clemens (see above) succeeded in his case with thymol after a sulfonamide had failed. Of course latterly sulfadiazine has been the most used of this group of agents.

Penicillin.—The record of this new agent in the treatment of actinomycosis has not been brilliant. In Hudson's (1943) case an actinomycotic infection of

the neck relapsed with the primary organism still present while under penicillin treatment although the secondary staphylococcus infection was eliminated. In the comprehensive penicillin report of Keefer *et al.* (1943), three cases of actinomycosis were included with a record of two deaths and one "improved or cured." Lyons (1943) reported four cases temporarily improved but felt that further observation would be necessary.

Surgery.—It is now the consensus that surgery should be boldly and persistently employed wherever the involved tissues can be radically curetted or widely excised. Wangensteen (1938) said that having set out a few years ago at the University of Minnesota to make a comparative study of iodides, surgery and irradiation, he obtained such satisfactory results with surgery that he never got around to trying the other measures. Furthermore, he learned that mere curettement and keeping the wound open by packing is just as effectual as excision. Cutler and Gross (1940) felt that the advances made in thoracic surgery in recent years justify very bold attempts to save life in apparently doomed pulmonary cases.

X-ray.—Roentgenologists are beginning to think very well of their results not only in the apparent but in the deep-seated lesions also. Auster (1940), in a review of the entire subject of actinomycosis, expressed the opinion that x-ray will undoubtedly play a more important part in the handling of this entity as time goes on. Cutler and Gross felt that the relative innocuousness of the procedure often makes trial of x-ray worthwhile. In the case of Rashbaum and McIntosh (1944), in spite of hysterectomy and bilateral salpingo-oophorectomy followed by large doses of potassium iodide, there was prompt recurrence in the abdomen; roentgen ray treatment resulted in disappearance of the recurrences.

Miscellaneous Measures.—None of the following have consistent successes to recommend them: colloidal gold, colloidal copper, copper sulfate, nonspecific protein therapy, autogenous vaccines.

Blastomycosis and Bronchopulmonary Moniliasis

Blastomycosis is an infectious but apparently noncontagious disease caused by a number of closely allied species of fungi, which may be called here the *Blastomycetes*. The impression that most cases in the United States have been reported from the vicinity of Chicago and from the state of Louisiana seems to be false, for though many cases have been seen in both Illinois and Louisiana, there is a wide scattering of reports throughout the country. The disease is known elsewhere in both hemispheres, but Moore (1938) divided blastomycosis into three types, North American, European and South American. The subject, as shown by Smith (1941), is becoming very complex; the studies of Conant and Howell (1942) convinced them that the North and South American varieties of the disease are caused by separate species of fungi.

Blastomycosis, as we know it in this country, affects usually the skin only, but deep-seated involvement of the long bones and of any of the internal organs, especially of the lungs, occurs not infrequently. Jacobson and Dockerty (1943) reported four cases in which the epididymis was involved, the condition clinically simulating tuberculous involvement of that structure. The cutaneous lesions take the form of papules, pustules, nodes, abscesses, or ulcers, and this form of the disease runs a course of many years during which active and quiescent periods alternate; when there is involvement of internal organs the prognosis is very bad. In the pulmonary cases the presenting symptoms are usually

not easily distinguishable from those of tuberculosis. Some of these bronchial and lung involvements are not strictly blastomycotic in origin but are due to yeasts of the genus *Monilia:* they are therefore separately designated "bronchopulmonary moniliases."

THERAPY

Iodides are used in large dosage here as in actinomycosis. Martin and Smith (1939) warned, however, that they may occasionally do harm in a patient who has become allergic to the infecting fungus. They therefore routinely skin-test their patient with *Blastomyces* vaccine and if he is hypersensitive they desensitize him with gradually increasing doses of vaccine before beginning the use of iodides. Bush (1941) felt that the improvement in his case was due to supplementing large oral dosage of iodides by the daily intravenous administration of 15 minims (1 cc.), later increased to 30 minims (2 cc.), of compound solution of iodide (Lugol's solution) plus 15 grains (1 Gm.) of sodium thiosulfate; x-ray therapy was simultaneously employed in this case. Most skin cases yield to iodide therapy if it is begun before there is involvement of the deeper structures, and if it is persisted in sufficiently long. Balina *et al.* (1944) reported a case in which arrest of the destructive skin lesions was apparently initiated by the local and systemic employment of sulfathiazole. In those rare cases where it is possible, total excision of the affected part is possibly the ideal treatment, but according to some observers it must be excision and not merely curettement, for this latter procedure is thought to have been responsible at times for a spread of the disease. Copper sulfate has been used effectively in some cases in doses of $\frac{1}{4}$ to 1 grain (0.015 to 0.06 Gm.) three times daily by mouth. Recently, x-ray therapy seems to have proved itself definitely useful, as cited above in Bush's case; irradiation in conjunction with iodides was apparently successful in two of the four cases of blastomycotic epididymitis of Jacobson and Dockerty (1943), but Hemphill and Noojin (1942), while feeling that this type of therapy is likely to be effective in skin cases, thought that it might be expected to be unavailing in deep lesions with bone involvement. Hedge (1928) reported 2 cases in which complete cure without any sign of recurrence in more than a year was accomplished by the application to the lesions of carbon dioxide snow under moderate pressure for ten to fifteen seconds. Pupo's (1928) 4 cases were successfully treated with intravenous injections of 10 cc. of 1 per cent methylene blue, or alternated with injections of 5 cc. of 0.5 per cent trypaflavine (acriflavine), according to the seriousness and obstinacy of the case.

In the disseminated form involving the internal organs all therapy seems to be hopeless, the success with iodides in a single pulmonary case of both Decker (1939), and Wylie and De Blase (1944), and with ether in the case reported by Fishman (1944), probably being the exceptions to prove the rule. However, perhaps I should state here just what Fishman did since his treatment was of a new type and the results very astonishing. Ether was applied locally to the skin lesions and was used to irrigate the osteomyelitic infection of the bone; in addition, 4 ounces of ether in an equal amount of oil were given rectally after a soapsuds enema on nine consecutive days. Thereafter the rectal ether-oil was given every other day for one week and then once weekly until the patient was discharged from the hospital, improvement having been constant and there being no evidences of any infection at the time of discharge; upon autopsy following death from another cause several years

later there were found no evidences of blastomycosis nor any pathologic effects from treatment. In the case of Solway *et al.* (1939) large doses of a sulfonamide were used without any obvious effect. Steinfield (1931) recommended yeast vaccines in pulmonary cases, and Bakst *et al.* (1934) used an autogenous monilia vaccine with satisfaction in a single instance. Flinn *et al.* (1935) thought that the substitution of milk sugar for all commercial sugars was probably helpful in one of their monilia cases.

Chromoblastomycosis

This is a fungous disease of world-wide distribution but of rare occurrence. Binford *et al.* (1944) reported what was apparently the tenth case in the continental United States, but Emmons *et al.* (1941), in reporting the sixth case, considered it likely that numerous other cases have hitherto gone unrecognized. This mycotic infection, with *Hormodendrum pedrosoi* or several related organisms such as *Phialophora verrucosa* in the causative role, has been much studied by Carrion and his associates in Puerto Rico and Moore and his group in Argentina. Pardo-Castello *et al.* (1942), confirming Weidman's earlier statement that this disease was being encountered in Havana also, reported 31 cases observed in Cuba. Classically the disease, which is often associated by the patient with injury by wood or vegetation, presents as a slowly progressing group of pink or violaceous, verrucous or papillomatous lesions, usually on the legs or feet; there are often cauliflower-like excrescences which readily ulcerate. But many of the cases have differed widely from this description so that apparently clinical recognition of the entity without laboratory aid is not easy; some dermatologists feel that perhaps some cases now being diagnosed blastomycosis are in reality chromoblastomycosis.

THERAPY

It has been the impression that these cases often respond well to iodides but these classical agents were found worthless by Pardo-Castello; he prefers intensive roentgen therapy for the superficial types and electrocoagulation for the more extensive and infiltrated conditions. Conant *et al.* (1944) stated the opinion that amputation should not be done since the lesions rarely become infected secondarily and the disease does not become generalized.

Sporotrichosis

Sporotrichosis is an infectious disease caused by a fungus of the genus *Sporotrichum*. In the two regions from which until recently most of the case reports have come, namely France and the Upper Mississippi Valley of the United States, the majority of the patients have been farmers or those otherwise in intimate contact with shrubs or the soil, but in 1942 Du Toit reported an "epidemic" of 650 cases among men working in a certain shaft of a mine in South Africa.

Sporotrichosis is characterized by the appearance of a subcutaneous nodule which attaches to the skin, breaks down in the center and becomes chronic as a cold abscess whose periphery remains well defined and indurated. A number of these lesions may appear on widely scattered portions of the body, but it is more usual for an ascending lymphangitis to develop from the primary nodule (the "chancre"), with numerous lesions appearing along its course. Montgomery and Holman (1938) emphasized the fact that pseudo-epitheliomatous changes may cause malignancy to be suspected in some of these cases.

The disease is usually chronic and in the United States the inflammation is of so low an order that there is little pain and practically no disturbance in the general health, but in France it would seem that radical amputations are often necessary and that visceral involvement is frequent (possibly their cases are not all truly the entity we recognize here as sporotrichosis?).

THERAPY

Here again the iodides in large doses are usually curative. Du Toit (1942), who used potassium iodide effectively in all of his 650 cases, started usually with 15 grains (1 Gm.) three times daily and worked up to 1 drachm (4 Gm.) daily. Such a case as that of Ray and Rockwood (1942), which was utterly resistant to the iodides, is rare but admittedly the use of these agents must be persisted in for a considerable time after apparent cure to prevent recurrence. Wade and Matthews (1938) successfully treated a patient through pregnancy and delivery without any effect upon the infant. Such tempting surgical procedures as radical incision or curettement should be avoided as they only prolong the process. However, abscesses which show no tendency to resorption are sometimes aspirated with advantage; it is the practice usually to refill the cavity with a weak iodide solution (1 per cent). It is said that x-ray treatment sometimes hastens the disappearance of the lesions but this is looked upon by most men as merely adjunctive therapy.

STREPTOTHRICOSIS

This is a very rare disease caused by a fungus-like organism called, perhaps erroneously, *Streptothrix*. In the small number of cases reported the lungs have been principally involved, though in a few there was implication of other organs as well. The symptoms are those of pulmonary tuberculosis, abscess and bronchopneumonia—a confusing picture. I believe that all proved cases of streptothrix infection have terminated fatally.

THERAPY

I know of nothing to describe.

COCCIDIOIDOMYCOSIS

(*Coccidioidal Granuloma and Paracoccidioidal Granuloma, Almeida's Disease*)

This disease is caused (in North America at least) by the fungus, *Coccidioides immitis*. In the United States the first recognized endemic area was the southern portion of the San Joaquin Valley in California, but it is now known that cases can be contracted along the western slopes of the Coast Range in the coastal counties and in Southern California inland from the Pacific. It seems also that Southern Arizona is badly infected and that Southern Utah, West Texas and probably New Mexico are also endemic areas. A large number of cases of a similar disease have been reported from the dry Chaco region of Argentina-Uruguay where the causative agent seems to be a radically different fungus, *Paracoccidioides braziliensis;* Jordan and Weidman (1936) proposed for this latter disease the designation "paracoccidioidal granuloma (Almeida's disease)." Dickson's studies, begun in 1937, introduced the viewpoint, for which ample confirmation has now been found, that "valley fever" of the San Joaquin Valley is the primary acute manifestation of the coccidioidal infection. In this malady the patient comes down with acute respiratory infection,

high fever, chills and night sweats, great prostration, anorexia of such degree that as much as 30 pounds in weight may be lost in a short period of time, backache and sometimes signs indicating meningeal involvement. In some instances a fine generalized rash occurs during the early days and in a small proportion of cases there may later appear erythema nodosum with or without erythema multiforme, phlyctenular conjunctivitis and severe arthritic pain without fluid or swelling in the joints. During the acute attack pulmonary cavitation may occur but the infection is usually well focalized and is rarely discovered. In 1940, Smith reported 432 diagnosed cases of this "valley fever" that had occurred in a period of seventeen months; the largest single epidemic that I have seen described was that of Goldstein and McDonald (1944) which involved 75 patients in one of the Army posts during War II. Sometimes recovery from the acute attack occurs quite promptly but in many instances the illness lasts for a number of weeks before terminating in the form of an arrested infection of an essentially benign nature. Smith (1943) said that sensitivity to the inhaled fungus as manifested by a reaction to coccidioidin develops ten days to a month and a half after infection is acquired, the incubation period from inhalation of the fungus to the development of the acute symptoms seeming to lie between seven and twenty-one days.

In addition to frank cases of the nature described above there must be many inapparent affections, for four fifths of the long-time residents of the San Joaquin Valley have been found to have positive skin tests, and infection of cattle, sheep, dogs and small rodents has been shown to be very common in the endemic areas. It seems that the recovered individual retains a high degree of immunity and will still react vigorously to coccidioidin for nearly thirty years after he has left an endemic area. Demonstration of the fungus in the sputum in the acute stage is said to be very difficult, but during this stage the sedimentation rate is accelerated, and Smith (1943) said that serological tests using coccidioidin as antigen for precipitin and complement fixation tests have proved very useful. It is now estimated that in not more than 1 infection in 500 or 1000 does the fungus disseminate, but when this dissemination does take place it usually occurs in a few weeks or months after the infection has been acquired except in the rare instances in which it occurs in the initial illness without any interlude. Dissemination means the development of the classical coccidioidal granuloma, which is looked upon as a disastrous occurrence. The symptomatology of the progressive form of the disease of course depends upon the sites to which the fungus has spread. According to Smith (1943), there will at times be a miliary spread and every organ as well as the meninges will be involved, while there is another more chronic form in which the symptoms are indistinguishable from those of tuberculous meningitis without other evidences of dissemination. However, in the main the mimicry of tuberculosis seems to be very close since there occur involvements of bones and joints, trachea, peritoneal cavity, lymph nodes and even the occurrence of verrucous skin lesions, but it seems that coccidioidal enteritis does not occur nor has anything exactly comparable to tuberculous nephritis been reported. Demonstration of the fungus in the sputum is said practically always to be possible in this progressive form of the disease.

THERAPY

In the acute form of the disease no form of specific chemotherapy has proved effective. Smith (1943) said that none of the sulfonamides was useful nor was

thymol or iodide; Goldstein and McDonald (1944) also found sulfonamides of no value in the treatment of their large epidemic, but in 2 patients who were treated with high titer convalescent blood there occurred almost immediate improvement. Michael *et al.* (1944) failed with both the sulfonamides and penicillin in their single case. Symptomatic treatment, and especially rest, are indicated. Smith (1943) said that except for isolation, which is not necessary since the disease does not spread directly from man to man, the patient should be treated as though he had tuberculosis until he has recovered clinically, his sedimentation rate is well back to normal, his roentgenogram indicates that any lesions are regressing steadily and the titer of the serological test is low or falling. His opinion was that if a pulmonary cavity has not closed after a few weeks of rest pneumothorax should be attempted but that it is inadvisable to resort to more radical measures. In the progressive cases, *i.e.*, the true "coccidioidal granuloma," among the medicinal and other agents each of the following has one or two successes to its credit and many more failures: (*a*) iodides; (*b*) intravenous dyes; (*c*) colloidal copper, the 5-cc. ampule intramuscularly at four-day intervals; (*d*) autogenous vaccines and foreign protein shock therapy (Jacobson, 1939, described some successes with a vaccine he prepares in Los Angeles); (*e*) thymol by mouth, beginning with 15 grains (1 Gm.) daily and working up to four times that amount until a total of 104 Gm. has been given in twenty-four days, administered (50 per cent) in olive oil in capsules during meals, 33 per cent used for irrigation also (Sox and Dickson, 1936); (*f*) tartar emetic and x-rays: the antimony potassium tartrate from 2 to 8 cc. of a 1 per cent solution intravenously on alternate days; ½ skin unit of unfiltered roentgen rays at ten- to fourteen-day intervals (Tomlinson and Bancroft, 1934). It was not apparent that the sulfonamides, penicillin or atabrine were of much value in the cases of Denenholz and Cheney (1944). In an occasional case early and radical amputation has cured a single lesion, but unfortunately other lesions occur elsewhere due to the disseminating nature of the process.

MADUROMYCOSIS

(*Madura Foot, Mycetoma*)

Maduromycosis is a chronic affection of the foot, occasionally the knee or thigh or buttocks and much more rarely the hand, caused by fungi of a number of different genera and species. It has been known since time out of mind in India, where it was first scientifically described, and is reported rather frequently from many other tropical countries. However, its occurrence is by no means confined to these warm regions for it has been recorded all over the world. Symmers and Sporer's (1944) report of a case seems to bring the total number observed in the United States up to 42, but there is reason to doubt that some of these, particularly the earlier reported cases, were truly maduromycosis.

The disease usually follows a penetrating wound, most frequently in a barefooted person, and practically always in a rural area. Following an incubation period thought to be between two weeks and three months, the fungus grows within the deep tissues and causes necrosis which eventually reaches the surface. The typical lesion is a deep sinus that is discharging a foul-smelling oily fluid containing certain characteristic grains. The whole foot may be riddled with a network of intercommunicating sinuses of this sort and is much swollen and characteristically deformed. Pain is usually of a dull aching sort and con-

stitutional symptoms are slight and inconstant. The disease may last many years; there is no tendency to heal.

THERAPY

Internal medication is a failure. Local measures are of no avail. Amputation is the only treatment of value. I think I should add, however, that Dixon (1941) successfully used sulfanilamide internally in a case which had the physical characteristics and clinical course of maduromycosis, though the attempt to culture the organism was unsuccessful; but in Fienberg's (1944) case the sulfonamides failed.

TORULOSIS

(*Cryptococcosis*)

It is only in recent years that distinction has been drawn between cases of torulosis, coccidiosis and systemic blastomycosis. The 6 cases reported by Reeves *et al.* (1941), together with the 6 cases that have since been reported, brings the total number up to 87, but it is considered likely that many times this number of cases have gone unrecognized. In most of the recorded cases infection has involved primarily the brain and cord with symptoms closely simulating tuberculous meningitis or brain tumor, with this difference that *Torula histolytica* (Mook and Moore say that *Cryptococcus* is the correct generic name) is usually abundantly present in the spinal fluid. In a few cases there have been cutaneous, joint, Hodgkin's-like, pulmonary and other visceral involvements; Robertson *et al.* (1939) very pertinently pointed out that an entity which can simulate a great many other maladies is worthy of more than passing interest to any practitioner. Tinney and Schmidt (1944) reported the ninth case in which there was generalized visceral involvement.

THERAPY

All the measures used in other mycotic infections are tried here but it is not a matter of record that any of them has been of the least avail. Pathogenicity seems to be relatively low until the central nervous system is involved and then the prognosis becomes immediately and absolutely bad; a few cases are recorded, however, in which self-arrest has seemed to occur for a short time at least. Marshall and Teed (1942) felt that one of the sulfonamides arrested the progress of their case, but Tinney and Schmidt (1944) thought it impossible to be certain that the drug was responsible for the symptomatic improvement in their patient.

HISTOPLASMOSIS

(*Reticuloendothelial Cytomycosis*)

In 1905, Darling found 3 cases in the Canal Zone which presented a clinical picture somewhat similar to visceral kala-azar but from which he obtained the organism *Histoplasma capsulatum*, since determined to be a fungus. The entity, to which in the course of time the title "histoplasmosis" has come to be applied, is a very complex and puzzling one and hence the number of reported cases rose very slowly for a number of years. Meleney, thoroughly and authoritatively reviewing the subject in 1940, brought the total of cases up to 32, but since that time cases have been reported with greatly increasing frequency. The first identification of the disease before death was accomplished

by Dodd and Tompkins in 1934. Also in 1934, De Monbreun cultured the organism, though actually in 1933 Hansmann and Schenken had reported a case from which they cultured an organism which they classified in the genus *Sepedonium* though stating that it resembled Darling's organism—many mycologists now consider that these workers were also dealing with *H. capsulatum*. The organism is transmissible to numerous laboratory animals and was recovered from a naturally acquired case of the disease in a dog by De Monbreun (1939), by Thuringer (1944), and by Callahan (1944), the first of these observers making the interesting suggestion that perhaps in histoplasmosis there is still unrecognized a common and milder form of the disease in man comparable to "valley fever" in coccidioidomycosis.

According to Meleney the clinical picture may resemble that of kala-azar, Hodgkin's disease, leukemia, lymphosarcoma, aplastic anemia, or pulmonary or miliary tuberculosis; or it may begin as a small skin lesion which develops into a generalized ulcerative skin condition. In the case of Henderson *et al.* (1942) the important clinical and pathologic features were those of ulcerative enteritis; in the case of Pernis *et al.* (1943) the symptoms caused by the fungus infection of the larynx were the cause of the patient's chief initial complaint though eventual destruction of the suprarenal glands caused death in the classical syndrome of Addison's disease; in the case of Broders *et al.* (1943) the clinical course, laboratory and physical findings were identical to those accompanying subacute bacterial endocarditis. Since the organism may be demonstrated with proper technics in the blood and in the tissue cells, obviously the diagnosis rests upon having this "new" disease in mind in a puzzling case which does not easily fall into one of the other categories.

THERAPY

Few cases have been recognized while there might still have been chance for effective therapy, so there is little treatment to describe. The iodides and arsphenamines seem to have been of little value. Meleney (1940) believed that antimony deserves special trial, either as antimony sodium tartrate (tartar emetic), or as pentavalent compounds as used in kala-azar, or trivalent compounds as used in bilharziasis. Both Rhodes *et al.* (1941) and Anderson *et al.* (1941) failed to halt the progress of the disease with sulfonamides, but the case of Balina *et al.* (1944), in the Argentine, in which the symptoms were mucocutaneous, arrest seemed to follow the local and systemic employment of these drugs.

OROYA FEVER AND VERRUGA PERUANA

(Carrion's Disease)

Carrion's disease had until recently been thought to be peculiar to certain cleft valleys on the western slopes of the Peruvian Andes, where it manifests itself in two forms: one, Oroya fever, a constitutional and fatal malady, and the other, verruga peruana, a cutaneous and less fatal affection. It has been endemic in this region since early historic times. Many of Pizarro's invading troops were at one time thought to have perished of this disease but now it is not certain that they did so; in more recent times it has taken a heavy toll in all the heroic railway building ventures that have taken place in these cruel

mountains. The latest recorded outbreaks of the disease occurred in southern Colombia and in Ecuador, the former comprising an epidemic in which there were 1800 deaths in about 4000 cases. The first Harvard Commission, formed to study the matter in 1913, cast considerable doubt upon the common causative factor in the two conditions, but this was dispelled by the work of Noguchi, Battistini and Hercelles, in 1926, who cultured *Bartonella bacilliformis* from the blood of an Oroya fever patient and produced Oroya fever or verruga peruana in monkeys by inoculating them with this culture, the particular manifestation produced being entirely dependent upon whether the intravenous or the intradermal method was used. They also produced Oroya fever by inoculation of material taken from a verruga nodule and obtained a pure culture of the organism from the blood of the inoculated animal.

Certain sandflies of the genus *Phlebotomus* have been almost completely convicted as the vector since, according to Hertig (1942), the disease has been transmitted to monkeys by the bite of wild infected sandflies, but the crucial experiment of transmission from man to man by the bite of the fly has not yet been performed. Certain plants and numerous animals both domestic and wild are suspected of acting as a reservoir for the causative organism; one thing is certain, that if a stranger leaves the endemic valley while it is still daylight he is almost sure not to contract the disease since this sandfly is a night feeder. The incubation period is from two to three or more weeks; it was twenty-one days in the experimental infection of the young student, Carrion, who died a martyr to his investigations. The studies of Howe (1943) made it appear unlikely that agglutinins play any major part in the almost universal acquired immunity which follows a typical attack of the clinical disease or in the apparent immunity which seems to be present in some long-term residents of endemic areas who deny past history of the disease.

Oroya Fever.—This type of the disease is characterized by a rather abrupt onset with weakness, malaise, slight rigors, moderate irregular fever and a rapid pernicious anemia with the parasites present in the red blood corpuscles. The mortality is variously estimated at from 40 to 80 per cent, but as many of these patients are affected with other chronic tropical diseases at the same time it is perhaps unfair to ascribe all the deaths to uncomplicated Oroya fever. The study of Ribeyro (1932) indicated indeed that the prognosis is favorable in simple uncomplicated Oroya fever and that the only complication which makes death almost certain is due to paratyphoid B bacillus. The fatal cases run their course in a few weeks.

Verruga Peruana.—This type is characterized in the beginning by joint pains and a moderate fever of short duration, after which the eruption appears. This eruption is at first miliary and is usually confined to the arms and legs, but it may occur elsewhere on the body and even on the mucous membranes. In most cases the rash becomes papular and subcutaneous nodules appear. Some of these nodules, attaching to the skin and ulcerating, are called "verrugas" and have given the disease its name. The mortality is also high in this type, but individuals who are not harboring other malicious tropical diseases at the same time nearly always recover. Only the ulcerated lesions leave any scars. Fox (1935) described the dermatologic lesions in detail.

THERAPY

Despite the havoc which Carrion's disease has wrought and the interest it has aroused in the modern scientific mind, no effective treatment has been

devised. Strong (1940) said that it was the consensus among conservative physicians in Peru that the arsenic-antimony compound, Sdt. 386 B, which was said by Kikuth (1937) to have been used successfully, is not of value. Patino-Carmargo (1939) and Groot *et al.* (1942), the latter in an exhaustive review of the Colombian epidemic, mentioned such agents as vitamins, calcium, antimony, arsenic, iodine, liver extract, blood transfusion, autohemotherapy, etc.—the usual list of agents when specific therapy is not at hand. Howe (1943) produced immune serum of high agglutinin titer in rabbits and injected three patients with severe Oroya fever with this serum but without dramatic therapeutic effects. The studies of Howe and Hertig (1943) indicated that vaccination with preparations of formolized suspensions of *B. bacilliformis* might definitely ameliorate the course of potentially serious cases though it seemed unable to prevent the development of the disease. I do not know if Ribeyro's work (see above) has been discredited, but if it has not been then the necessity for protective vaccination against typhoid-paratyphoid organisms of all persons who are obliged to visit Oroya-infested regions is quite evident.

PLAGUE

There are five major infectious diseases whose entire handling has been taken over quite properly by public health authorities or other specialists of great experience. These five are Asiatic cholera, leprosy, plague, trypanosomiasis and yellow fever. Since they do not nowadays raise problems in treatment for the general practitioner, I shall no longer allot space to a consideration of them in this book.

PNEUMONIA (TYPICAL)

While recognizing that the differentiation between lobar and bronchopneumonia is not always easy, indeed sometimes impossible, to make at the bedside, I am describing the disease below in these two classical forms because both presentation and understanding are thus facilitated.

Lobar Pneumonia.—Lobar pneumonia is one of the most widespread and dangerous of all the infectious diseases of the temperate zones. Its occurrence in the tropics has been thought to be relatively rare save in certain restricted areas where extreme undernutrition makes the native population especially susceptible; however, Mumford and Mohr (1944) reported a high incidence of pneumonia in the native populations throughout all of the Southwest Pacific area and one wonders whether inadequacy of the dietary explains the incidence in those regions also. In about 90 per cent of instances it is caused by *Diplococcus pneumoniae*, in the remaining cases by streptococci, staphylococci, Pfeiffer's bacillus (*Hemophilus influenzae*, which incidentally does not cause influenza); very rarely Friedländer's bacillus (*Klebsiella friedländeri*) is responsible, but in these instances the physical findings are not entirely typical of the lobar form of the disease. Dubin and Kerby (1943) described a case of pneumonia studied at autopsy in which it seemed reasonably certain that the etiologic agent was *Escherichia coli*. Levine and Plattner (1944) described three

cases in which pneumonia was diagnosed before *Salmonella suipestifer* was isolated from the blood. Serums are now available for the identification of 33 types of *Diplococcus pneumoniae*. During ordinary (*i.e.*, nonpandemic) times, Reimann (1935) found the most ordinarily encountered types to be I, II, III, VIII, VII and V, in approximately that order, while Bullowa and Gleich (1938), studying 3817 cases at Harlem Hospital over a period of seven years, found the order to be I, III, II, V, VIII, VII and IV in adults; among infants and children, XIV and VI also occurred frequently. Recent studies have shown that the type of organism present in the mouth of most individuals is not the one responsible for most cases of the disease; present knowledge therefore inclines toward the position that pneumonia is contracted from an active case or from a recovered case still harboring the causative organism, or from an individual who has become a temporary carrier following such contact. Finland (1942) concluded as a result of his exhaustive study that carriers probably account for the bulk of infections in the community. Only one group so far as I am aware (Benjamin *et al.*, 1939) has as yet advocated that pneumonia be treated, and inferentially quarantined, as a contagious disease by public health officials. Recent head cold or grippe, exposure to wet and cold, and ecxessive fatigue are frequent precursors of the disease; the incidence is decidedly higher among blacks than whites. The average mortality before the advent of effective chemotherapy was: private practice, 15 (!) to 25 per cent; good general hospitals, 25 to 35 per cent; public institutions treating the lowest classes, including many acoholics, 50 to 60 per cent. But these were the statistics from metropolitan areas; country practitioners always maintained that their mortality was much lower than in the cities—Simons' (1942) study indicated that the mortality in the average rural American community is certainly no higher than that of urban and teaching centers. In general the mortality trend has been downward throughout the world during a long period of years much antedating specific therapy.

Lobar pneumonia is often but not invariably characterized by the suddenness of its onset, typically with a chill, stabbing pain in the side, high rise of temperature and pulse rate, rapid respiration often with dyspnea, cough and rusty sputum, and involvement of the nervous system ranging from mere anxiety to active delirium. Herpes simplex, jaundice (possibly of more frequent occurrence in Negroes than in whites and likely due in them, in the opinion of Turner *et al.* [1943], to improper nutrition) and initial vomiting are often seen. There are typical physical "findings" in the chest, whose description has no place here. Cyanosis, varying in degree with the respiratory and circulatory involvement, always makes its appearance later. In the average case, if not treated by the newer specific methods, the symptoms last for from five to ten days with very little remission and then the attack terminates by a gradual lessening in severity of all symptoms or, in less than half the cases, by a "crisis" in which the defervescence occurs within twenty-four hours.

Bronchopneumonia.—Bronchopneumonia is a diffuse lobular inflammation of the lungs in which several organisms can be identified as the causative factor. There are several types:

(1) Primary bronchopneumonia, occurring in children under four years of age. This type is not directly associated with any other disease, is usually mild, and is nearly always caused by pneumococcus; the symptoms are much like those of lobar pneumonia except for the difference in the distribution of the pulmonary lesions.

(2) Secondary bronchopneumonia is caused by staphylococcus, streptococcus, Pfeiffer's bacillus (*Hemophilus influenzae*), sometimes Friedländer's bacillus (*Klebsiella friedländeri*) and rarely the pneumococcus. It is the most dreaded complication of the infectious diseases in children and of the infectious and chronic debilitating diseases of middle and old age; many postoperative pneumonias and some post-traumatic pneumonias are of this type. The symptomatology of bronchopneumonia is too diverse and complicated to warrant description here; suffice it to say that the occurrence of this complication is usually marked by a change in the severity and finally the type of the symptoms which the patient is manifesting, until ultimately the respiratory and circulatory embarrassment, cyanosis, general toxemia and diffuse chest involvement of bronchopneumonia completely overshadow or supersede the original picture.

(3) Primary epidemic bronchopneumonia. The mortality is very great in these cases, as witness the epidemic during the first World War. Most of the postinfluenzal pneumonias of that dark period were caused by *Streptococcus haemolyticus*, with or without the accompaniment of other organisms whose virulence had been temporarily raised to a high pitch, but in more recent influenza epidemics the staphylococcus has also appeared as a complicating organism.

(4) Lipoid pneumonia, in which the congestive, inflammatory or necrotic changes are the result of the aspiration of milk fat, fish oil or liquid petrolatum in recumbent babies or debilitated adults or in healthy individuals who use medicated liquid petrolatum drops or sprays intranasally over a long period of time (see Cannon's, 1940, review for the literature). Differential diagnosis of this type of pneumonia in its acute form is rarely made antemortem.

In the aged, pneumonia is many times not clear cut in type; the onset may be insidious and the course, which is sometimes even feverless, may be very protracted; high incidence of preexisting circulatory and renal disease of course much increases the gravity of the situation.

THERAPY

The treatment of lobar and bronchopneumonia can be described together with such exceptions as will be noted later. I shall employ the following subdivision of the subject for convenience: sulfonamides; penicillin; serum in selected cases; oxygen therapy; nursing measures; dietetics, fluid and chloride administration; symptomatic treatment.

SULFONAMIDES

The history of these drugs in pneumonia has merely been a repetition of the history of all truly specific agents: to wit, there was never any doubt of their efficacy after the first early trials. Reports of their consistently successful use quickly poured in from all over the world, and the standardization of methods for their employment with the highest degree of safety and certainty lagged far behind the universality of that employment.

Routine Employment Warranted.—It has come to be practically universal custom to begin the administration of a sulfonamide in every case without exception in which the clinical diagnosis of pneumonia has been made. Indeed, these drugs are nowadays used so early in the cases that the actual reported incidence of the disease in the United States has declined very much in recent years. Morgan (1944) reported that the mortality of pneumonia in the Amer-

ican Army in War I was 28 per cent and in War II 0.7 per cent—a fine record surely but probably reflecting as much as anything the fact that the sulfonamides were used before most of the pneumonias really got started.

Effect Upon Mortality Rate.—As long ago as 1940, Finland made the point that the deaths still occurring in pneumonia are mainly in the very aged, in persons with complicating severe systemic disease, and in those in whom treatment is delayed until they are in a moribund state or focal infections have already become established. His prediction that we would be able to cut our mortality in the United States to one fourth or even less has certainly been borne out. In the study of Flippin *et al.* (1943), comprising the treatment of 1635 adults with pneumococcal pneumonia, the mortality was 10.6 per cent; lower figures than this have been reported to be sure, but the striking nature of this achievement at the Philadelphia General Hospital is only appreciated when it is further stated that the mortality in 1904 cases during the five years preceding the introduction of sulfonamide therapy was 40.1 per cent. Even among the very aged in institutions the sulfonamides are strikingly effective, for Kaufman (1940) reported a series of 81 such cases in which there was a fatal outcome in only 23.5 per cent though the expected incidence without the drug would have been 75 per cent. It seems to me that the truest indication of what can be accomplished under specially favorable circumstances was contained in Ordman's report as long ago as 1939: the case fatality rate from lobar pneumonia among about 300,000 native laborers in the Witwatersrand goldfields (mostly young individuals and under constant medical supervision) had been between 11 and 13 per cent for the five years preceding the introduction of the drug; under the sulfonamide the rate declined to 2.75 per cent.

Effect Upon the Patient.—The temperature turns sharply downward after the patient comes under the influence of the drug, often reaching normal within or before twenty-four hours and practically always under forty-eight hours; indeed if fever continues beyond forty-eight hours it is usually found that there is some serious complication or the pneumonia is of a rare type which is resistant to the drug. The respiratory and pulse rates and the leukocyte count also decline and the patient ceases to give the impression of one critically ill, but nevertheless he does not often show that striking change characteristic of normal unaided crisis (the physical signs may persist or even continue to develop for a time). Very occasionally there are added to his general "toxic" feeling the disagreeable reactions induced by the drug itself. Finland *et al.* (1942) found that the antibody response of patients treated with sulfonamides is in every respect comparable to that resulting from spontaneous recovery.

Effect Upon the Incidence of Complications.—Complications are certainly being seen much less frequently in this new chemotherapeutic era, but in the nature of things we shall probably not ever be able to prove the point sharply with statistical evidence. Two points, made by leaders in this field some years ago, are worth reemphasizing here: one is that we are likely nowadays to lose track somewhat of the prevailing types and severity of pneumonia because so many unrecorded cases are being treated in the home; and the other is that we may be seeing sequelae heretofore unknown because the patients who might have developed them in an earlier day all died.

Effect in Recurrent Attacks.—Strauss and Finland (1942) found that recurrences are not more frequent in patients treated with sulfonamides than in those not so treated but that there is a tendency in the drug-treated cases for

second attacks to occur with the same type of organism and at shorter intervals. In 24 adults given sulfonamide therapy on two or more occasions for recurrent pneumococcal pneumonia, Schwartz *et al.* (1942) found the drugs just as effective in the subsequent as in the initial attack.

Types of Pneumonia Affected.—These agents are of much wider application than serum because they seem to be equally effective in all the types of pneumococcus lobar pneumonia whether the case be of primary or postoperative or post-traumatic or other secondary origin. In the primary streptococcic and staphylococcic pneumonias the newer drugs in the series are also effective; Carey (1941) reported astonishingly fine results in pneumonias of this sort in infants and children, though he did not attempt in all instances a sharp distinction between lobar and bronchial involvements. In staphylococcic pneumonias occurring during an epidemic of influenza, Finland *et al.* (1942) reported that suitable benefit might be expected from the early and intensive use of sulfonamides except perhaps in some of the severe and fulminating cases. In the frank bronchopneumonias, although brilliant results are many times achieved, it is more difficult to assess the results in general, for, as Kinsman and Moore (1941) well emphasized, these pneumonias are so frequently terminal events in other conditions themselves tending toward fatality that it is difficult to know just how much has been accomplished with drugs. However, Plummer (1940) used the drug successfully in some of the most unfavorable pneumonias complicating heart disease, bronchiectasis, asthmatic bronchitis, emphysema and old age. In infancy and childhood the sulfonamides have a fine record even though many of these pneumonias occur as complications of other acute illnesses Plummer and Liebmann (1940) found the pneumococcus bacteremias, which are usually fatal if untreated, responding dramatically to these drugs and indeed felt that such a bacteremia, persisting after adequate sulfonamide administration, is usually due to a focus such as vegetative endocarditis. In mixed infections, particularly if Pfeiffer's bacillus (*Hemophilus influenzae*) is present, results have not been striking but the number of cases so far reported has been small. In infections with Friedländer's bacillus (*Klebsiella friedländeri*), both Finland (1940) and Hyde and Hyde (1943) said that the results have upon the whole been discouraging, though Solomon (1940) reported satisfactory responses in a very small series of cases of the chronic form of the affection which sometimes supervenes in the few patients who survive the acute attack.

Choice of Sulfonamides.—The two outstanding drugs for use in pneumonia at the present time are sulfadiazine and sulfathiazole, together with their soluble sodium salts for parenteral injection. Undoubtedly Plummer (1944) expressed the consensus in saying that sulfadiazine is to be preferred of the two because it is less toxic and the blood concentrations following its administration are more satisfactory. Several newer drugs have been reported upon very favorably, sulfamerazine by Flippin *et al.* (1943), sulfapyrazine by Ruegsegger *et al.* (1943), and sulfamethazine by Loughlin *et al.* (1944) and Melton (1944); but in the opinion of Plummer each of these three shows in some instances a sufficiently high degree of acetylation with a corresponding decrease in the free and active portion for the treatment on this basis to become ineffective. A definite advantage of sulfadiazine is its consistently low acetylation and hence potential, and probably actual, lower toxicity. Furthermore, the greater solubility of sulfadiazine in both its free and acetylated forms is a great advantage.

Sulfonamide Dosage.—In 1944, a Pneumonia Advisory Committee to the Department of Health of New York City made the authoritative statement

that the accepted dosage schedule for sulfadiazine and sulfathiazole consists of an initial dose by mouth of 60 grains (4 Gm.) followed by 15 grains (1 Gm.) every four hours until the symptoms have subsided and the temperature has been normal for forty-eight hours. In the case of sulfamerazine the schedule is similar except for a dosage of 15 grains (1 Gm.) every six to eight hours instead of every four hours. Where patients are seriously ill, or in the presence of vomiting, it may be desirable to substitute for the initial oral dose an intravenous dose consisting of 75 grains (5 Gm.) of the sodium salt of sulfadiazine or sulfathiazole, or 60 grains (4 Gm.) of sodium sulfamerazine, dissolved in a liter of physiological saline solution or in a 5 per cent solution of sterile distilled water. Solutions of these drugs in physiological saline solution may be given subcutaneously in concentrations of 1 per cent. Sulfonamide administration should be accompanied by an adequate fluid intake (3000 to 4000 cc. in an adult) and by the use of alkalis sufficient to maintain an alkaline reaction of the urine; for the latter purpose 90 grains (6 Gm.) of sodium bicarbonate have been recommended as an initial dose and 40 grains (2.5 Gm.) of the same agent every four hours as the continuation dosage for adults except when nephritis or other contraindicating disease is present. While the primary purpose of such therapy is to maintain a urinary output of at least 1200 to 1500 cc. per day, it is recognized that great caution must be exercised in the administration of fluid to patients with heart disease or to those who have evidence of congestive heart failure. Furthermore, Ohnysty and Wolfson (1944) pointed out that if there is a complicating cardiac insufficiency, potassium bicarbonate had better be substituted for sodium bicarbonate since the sodium ion promotes retention of fluids.

When the initial large dose of sulfadiazine is given the level of the drug in the blood stream reaches 4 to 6 mg. per cent in four to six hours but thereafter begins to diminish, hence the necessity to repeat the administration at four-hour intervals. It seems to be the consensus that a blood level of between 5 and 10 mg. per cent is desirable to obtain best results, and the above dosage scheme is certainly devised to maintain such a level, but as a matter of fact there is not much very convincing evidence, either experimental or clinical, that concentrations above 3 to 4 mg. per cent are needed. Therefore, since Plummer and Wheeler (1944) demonstrated in a study comprising a very large series of patients that the incidence of toxic reactions from the sulfonamides is directly proportionate to the size of the daily dosage and to the duration of treatment, it would seem advisable to consider the employment of smaller dosage than the above where feasible. Dowling *et al.* (1943) treated 81 unselected adults with pneumococcal pneumonia with an initial dose of 30 grains (2 Gm.) of sulfadiazine followed by 7½ grains (0.5 Gm.) every four hours until recovery was certain or death ensued, while an alternate group of 79 patients was given 90 grains (6 Gm.) initially, followed by 15 grains (1 Gm.) every four hours. The higher doses were slightly more often followed by rapid recovery than the lower doses and there was less likelihood of relapse, spread of the pneumonia to another lobe, or of delayed resolution in the patients receiving the higher dosage; nevertheless it was evidenced from this study that the smaller doses could be used without fear of an increase in the mortality rate or of serious complications. Plummer (1944) said that his own recommendation has been that, after the initial large dose, 15 grains (1 Gm.) is to be given every four hours but omitting the 4 A. M. or another of the night doses, so that the patient actually obtains only 5 instead of the usual 6 Gm. per day.

Perhaps, also, something additional should be said regarding alkali and fluid administration. At a *p*H of 7.5, acetyl sulfadiazine is the most soluble of the acetyl derivatives of any of the currently used sulfonamides. For example, at this reaction acetylsulfathiazole reaches a solubility of only 28 mg. per cent whereas acetylsulfadiazine is soluble to the extent of 512 mg. per cent. Sulfathiazole and sulfadiazine themselves are almost equally soluble in an alkaline urine (*i.e.*, *p*H 7.5) but—and this is the important point—acetylsulfathiazole is only four times as soluble in an alkaline as in an acid urine, whereas acetylsulfadiazine is more than 25 times as soluble under the same circumstances. The two outstanding facts here are the following: first, that urinary tract damage is certainly much less likely to occur with sulfadiazine than with sulfathiazole if the urine is kept alkaline, and second, that what is required is not just an arbitrary amount of alkali daily but the administration of sufficient in each case to maintain the urine definitely alkaline. Plummer (1944) said that when using sodium sulfadiazine parenterally he uses sixth molar sodium lactate solution about 1000 cc. daily. Finally, it should be mentioned that the attempt to prevent renal reactions by giving a high fluid intake has definite limitations as compared with alkalinization, since increasing the fluid intake two-fold can only double the amount of acetylsulfadiazine dissolved, whereas raising the urine from acid to alkaline in reaction will increase its solubility more than twenty-five times.

The rule of thumb dosage for children, as stated by Janeway (1943), is an initial dose of $\frac{3}{4}$ grain (45 mg.) per pound body weight, and then 1 grain (60 mg.) per day per pound divided into four or six doses, whichever is most convenient.

Sulfonamide Toxicity, Resistance, etc.—See the separate chapter on this subject at the end of the book.

Penicillin

As Primary Therapy in Pneumococcus Pneumonias.—Tillett *et al.* (1944) employed penicillin as the primary treatment in 46 cases of pneumonia which they believed were representative as to kind and severity. The mortality in the series was 6.5 per cent. Of the three patients who died, one was a sixty-nine-year old man with pneumonia and bacteriemia due to Type VIII pneumococcus and severe congestive heart failure; his blood culture was negative on the second hospital day and the temperature was below 100° F. (37.8° C.) but the heart failure was worse and he died thirty-six hours after admission. In the second fatal case the pneumonia and bacteriemia were due to pneumococcus Type I and were superimposed on some chronic pulmonary disease; here again the blood culture became negative on the second day but clinical improvement failed to follow. The third patient who died had pneumonia due to pneumococcus Type I but no bacteriemia; he did not appear severely ill but did not respond to penicillin and died on the third hospital day a few hours after the onset of pulmonary edema. Of the 43 patients who recovered, the improvement very strikingly indicated the great value of the drug in 39; but the response was not clearly defined in 4 patients, one of whom probably had primary atypical pneumonia and the other three unrelated underlying pulmonary diseases which prolonged their illness beyond the usual course of pneumonic resolutions. In the patients who responded well (84 per cent of the total) the impression was gained that improvement in all respects was accomplished somewhat more rapidly than under sulfonamides. As a result of their

experience, Tillett *et al.* suggested the following plan of treatment: in cases of moderate severity, 10,000 units of penicillin intramuscularly every three hours for four doses on each of three and possibly four successive days; for seriously ill patients, 25,000 units intravenously every three hours for the first two doses on the first day, followed by 10,000 units intramuscularly at three-hour intervals for the second two doses the first day, subsequent treatment of the second, third and fourth day to follow the plan outlined for cases of moderate severity.

In Sulfonamide-Resistant Pneumococcus Pneumonias.—Tillett *et al.* (see above) treated two cases of lobar pneumonia and bacteriemia due to pneumococci refractory to sulfadiazine; both the patients responded very promptly despite the fact that one had lymphatic leukemia and the other case was complicated by empyema which had been surgically drained.

In Sulfonamide-Resistant Staphylococcal Pneumonias.—In four cases of this sort Bennett and Parkes (1944) employed penicillin without a single death though treatment was not begun until the twelfth, seventeenth, twentieth and twenty-first days, respectively.

In Empyema.—The sulfonamides, whether administered by mouth, parenterally, or intrapleurally, have not been satisfactory in the treatment of empyema developing as a complication of the pneumonias, but apparently penicillin is going to prove much more effective. Tillett *et al.* (1944) introduced penicillin into the infected pleural space in 8 patients with pneumococcal empyema; in 7, the infection was eliminated by the local therapy without requiring surgical drainage, 6 of them recovering completely with only a restricted area of pleural thickening remaining as a permanent alteration. As a result of their experience, these observers felt that 30,000 to 40,000 units of penicillin contained in 30 to 50 cc. of isotonic salt solution should probably be injected intrapleurally on alternate days for at least 3 doses; they felt further that it was advisable to irrigate the cavity with a few hundred cubic centimeters of physiologic saline solution after bedside aspiration before introducing the penicillin and to repeat the procedure if necessary at intervals of several days after treatment in order to hasten removal of the degenerated sterile exudate and minimize the reaccumulation of an effusion.

Bennett and Parkes (1944) successfully treated 2 cases of streptococcal empyema and 1 of staphylococcal empyema.

Details of Penicillin Employment.—See the article on Sepsis.

Serum in Selected Cases

Type-specific antipneumonococcic serum was before the profession for many years prior to the advent of the sulfonamides but it never came to be widely used for the following reasons: (*a*) the relatively small proportion of patients considered suitable for this type of therapy; (*b*) the general cumbersomeness of the procedure and the lack of reliable typing facilities in many nonmetropolitan areas; (*c*) the unwillingness of many physicians to impose the added burden of possible serum reactions upon their patients; (*d*) both the obtaining of the material for typing and the administration of the serum were particularly difficult in infants and children; (*e*) it was expensive; and (*f*) the evidence of a favorable effect upon the gross mortality in large series was not very convincing, though in some types a substantial reduction in mortality was undoubtedly achieved. The earlier studies in which both serum and sulfonamides were employed indicated somewhat better results from the combination than

could be obtained from the sulfonamides alone; but later studies, such as reported by Shackman and Bullowa (1943), and Plummer (1944), did not reveal any advantage accruing from the combined use of the two agents. Prompt responses to serum have been reported by Tillett *et al.* (1943) and Plummer (1944) in cases in which the pneumococcus was sulfonamide-resistant. In drug-sensitive individuals serum would also seem to be indicated, and indeed it seems not unlikely that both sulfonamide resistance and sulfonamide sensitivity will increase as the years go by, but Plummer (1944) undoubtedly expressed the consensus in saying that penicillin rather than serum is likely to be the agent chiefly called upon as a substitute for sulfonamides in the future.

In view of the fact that serum is now so little employed I shall confine myself to a very brief outline of the practical aspects of its use.

(*a*) *Concentrated rabbit serum* is now preferred to horse serum. It can be given in smaller volume for a given unitage, it is considered possibly able to penetrate tissues better because of the smaller size of its molecule, individuals previously sensitized with horse serum may be given rabbit serum, higher potencies can be obtained in some of the types than is possible in horse serum, rabbit Type XIV serum may be safely given, which is not true of horse serum of this type.

(*b*) I quote the report of the Committees to the National Research Council (1941) for a condensed statement of preliminary *tests for hypersensitivity:*

"Two tests for serum sensitivity are available, and it is frequently desirable to use both. The first consists of the intracutaneous injection of 0.1 cc. of a solution of the serum diluted 1 to 10 in sterile physiologic solution of sodium chloride. The reaction is positive if at the end of twenty minutes the wheal at the site of the injection has enlarged to the size of a nickel and has an area of redness about it. (I do not know how many agree with Volini and Levitt [1939], of Cook County Hospital, who consider this test often gives false positive reactions with rabbit serum.) The second test is the conjunctival test. This consists of instilling 1 drop of a 1 to 10 dilution of the serum in sterile physiologic solution of sodium chloride inside the lower eyelid of the patient. If redness and swelling of that eye appear within twenty minutes, the reaction is positive. A positive reaction can be countered easily by instilling 1 or 2 drops of a 1 to 1,000 solution of epinephrine hydrochloride inside the lower eyelid, a procedure which should be followed with all positive reactors in order to prevent the rare instances of corneal ulceration. These tests are interpreted as follows: If the ophthalmic and cutaneous reactions are negative, then antitoxin may be given by any route. A definite wheal-like reaction, with surrounding erythema, indicates cutaneous sensitivity. A positive ophthalmic reaction, with or without a positive intradermal reaction, indicates a probable systemic reaction. Serum should never be given if both the ophthalmic and the cutaneous reactions are positive and should be used only with the greatest of care if either the ophthalmic or the cutaneous reaction is positive."

Of course serum should not be given to any patient with a history of asthma, hay fever, food sensitiveness, urticaria, or angioneurotic edema, or to one who admits serious reaction to any previous serum injection.

(*c*) *Administration* is intravenous except to infants, in whom it is given intramuscularly. It is customary to give the first 0.5 to 1.0 cc. as a test dose, diluted with 9.0 cc. of saline and injected very slowly while watching the patient's color, pulse, etc. Some follow this rule: If after five minutes the pulse has risen 20 beats or the blood pressure fallen 20 points the patient should be considered sensitive; if, however, there has been no reaction in one hour after the preliminary dose the full dose may be injected, preferably at a rate not to exceed 1 cc. per minute; a syringeful of epinephrine (adrenalin) solution should be at hand in any case—indeed, Engelsher (1944) recommended that 4 to 8 minims

(0.25 to 0.5 cc.) of epinephrine solution be given subcutaneously ten minutes before any serum injection.

(*d*) *Dosage.*—The Committees reporting to the National Research Council (1941) recommended an adult initial dose of 200,000 units if the attack is in its early stages, 300,000 units if in an advanced stage, subsequent doses of 100,000 units every eight hours if necessary. This is of course high dosage but it is assumed nowadays that the serum is being given only when there are strong indications for its employment. For children the dosage is reduced somewhat; Carey (1940) gave from 30,000 to 60,000 units from infancy up to twelve years, but many men feel that above the age of two the dose should be at least 100,000 units, and 150,000 units if given intramuscularly. A few men have used the intracutaneous polysaccharide test of Francis as a guide to dosage, feeling that there is no certain clinical index of the point at which an adequate amount of serum has been given; but since its application requires special preparations not generally available, and the reaction is not serviceable at all in about 10 per cent of instances, I shall not describe it here.

(*e*) *Reactions.*—In the acute allergic reaction, occurring during or shortly after the administration, the patient becomes anxious, dyspneic, flushed and cyanotic, and the pulse is rapid and weak; often there is tightness in the chest and a desire to vomit, urinate and defecate. Epinephrine (adrenalin) controls all but a very small percentage of these cases. Chills and fever (the so-called "thermal reaction") may occur within fifteen minutes or after an hour and a half or more; adrenalin is of no use here and in some instances the usual treatment for hyperpyrexia may have to be instituted, and often it is necessary to treat the patient for shock also before the incident is over. It is said that acetylsalicylic acid (aspirin), given before injecting the serum, reduces the incidence of thermal reactions. Beeson and Hoagland (1938) obtained immediate cessation of the chill by giving 10 to 20 cc. of 10 per cent calcium chloride very slowly intravenously; there was no relief if the patient had previously received adrenalin. Urticaria, of either the small or giant variety, is seen relatively rarely with the refined serums now in use; adrenalin usually controls it. Engelsher (1944) advised that in order to avoid or minimize late serum reactions, ephedrine and phenobarbital be given two hours after the injection and their administration be repeated at three- or four-hour intervals for three to five days. Serum sickness may occur in four to twenty-one days after an injection but is usually mild nowadays.

(*f*) *Contraindications.*—In addition to allergic individuals and those who have previously had a severe reaction, serum should not be given to old and debilitated patients, to those in shock or with congestive heart failure, to those with acute pulmonary edema or those already moribund. It is wasted if given to a patient in whom there is a focus such as empyema.

Oxygen Therapy

The chief reasons in the past for the administration of oxygen in pneumonia were that (*a*) proper aeration of the blood is difficult in the normal atmospheric content of oxygen because shallow breathing does not permit full ventilation of the lung and consolidation and edema fluid prevent ready diffusion of oxygen into the capillaries; (*b*) cardiac effort is greater when there is a diminished supply of oxygen; and (*c*) the presence of fever calls for increased oxygen consumption. It has been felt that in addition to cyanosis (not seen in the very anemic individual even though there is a quite high relative anoxemia, and in

circulatory failure sometimes masked by pallor), oxygen deficiency may be manifested by considerable gastro-intestinal, respiratory, circulatory and central nervous system disturbances, and that, therefore, in most cases of pneumonia the therapeutic administration of oxygen in a concentration of 50 to 60 per cent had best be begun as soon as possible. Indeed, for a good many years the routine administration of oxygen in pneumonias was a matter of course in many hospitals with the wealthier type of clientele, and a good many physicians felt they were extremely remiss if they did not use the gas in every case even though the apparatus had to be hauled to the home. However, so far as I am aware, there has never yet been published any satisfactory proof that oxygen therapy is life-saving no matter how much better the patient may look and possibly feel under its influence. It is terribly expensive therapy, and of course has not held its own in the new chemotherapeutic era; Plummer was able to say, in 1944, that "oxygen occasionally has great value but now is desirable in only a small percentage of the cases."

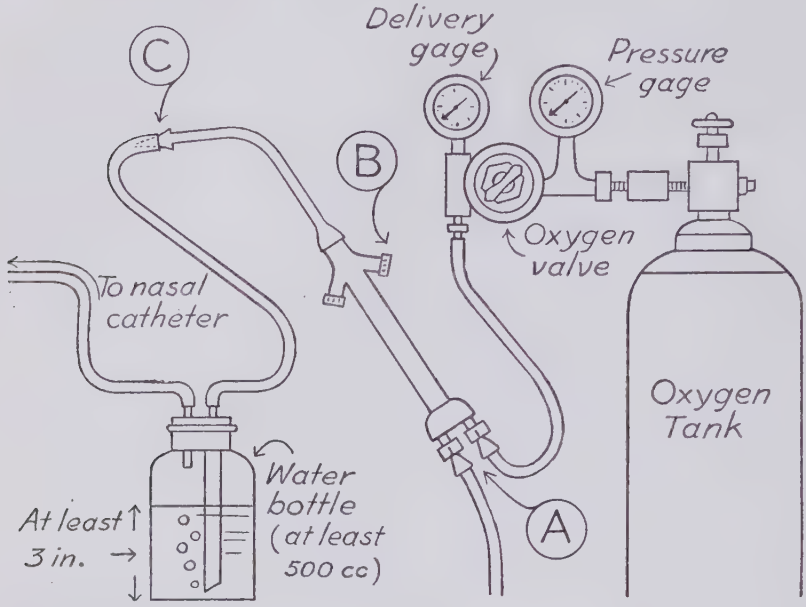
In place of the completely enveloping tent, which is greatly objected to by many patients and is extremely difficult to operate, numerous hospitals have one or the other of the several types of face mask or hood which have been devised. Each of these has its advocates, of course, and they are probably all fairly satisfactory, but it seems that most oxygen is still administered, whether in homes or hospitals, by either the nasal catheter or nasal inhaler methods.

Nasal Catheter Method.—A special nasal catheter may be used but the ordinary urethral soft rubber catheter, No. 10 to 14 French, is just as good provided that several holes are cut in it at intervals of ½ inch. Following the directions of the Committee on Inhalational Therapy of the New York Academy of Medicine (1943), one should insert the catheter, lubricated with KY jelly or petrolatum, into the nostril for a distance of approximately 3 inches, that is up to but not touching the posterior wall of the nasopharynx. Five liters of oxygen a minute will usually provide 37 per cent of oxygen in the inspired air with a catheter in this position. If the catheter is passed down into the oral pharynx opposite the glottis, a concentration of 42 per cent oxygen may be obtained at a flow of 5 liters a minute, but it should be remembered that oxygen may pass into the stomach and distend the abdomen if the catheter is placed lower than the uvula. The catheter is supported and held in place by bringing it up over the nose and fastening it with adhesive tape to the forehead or cheek. The advantage of using only one catheter at a time is that a fresh one can be introduced into the other nostril before the old one is removed, a fact of great importance in a patient attuned to oxygen concentrations higher than normal; replacement should take place every twelve to twenty-four hours, more often if the quantity of mucus necessitates it.

Nasal Inhaler Method.—The inhaler is a metal Y-tube (malleable, so that it can be bent for individual adjustment) with plugs on the two ends of the Y much like those on the earpieces of a stethoscope. It is so shaped that when the plugs are in the nostrils the stem of the Y lies up over the middle of the forehead where it may be fixed in place by adhesive or a suitable strap. When using the inhaler, about the same alveolar oxygen concentration is accomplished at a given flow rate as with the nasal catheter (see above); children will rarely tolerate a flow of more than 2 liters by either method. Even the most cooperative patient often cannot refrain from pulling the inhaler plugs out of place because of the irritation they cause.

Oxygen Supply.—Tanks of commercial oxygen as used by welders are just

DIAGRAM AND TABLE FOR CONVERSION OF OXYACETYLENE WELDER INTO APPARATUS FOR DELIVERY OF THERAPEUTIC OXYGEN



At A disconnect tube from acetylene tank.
At B open the valve fully and leave it open.
At C read the standard size number of the welding tip.
Apply to the Table to learn what the oxygen delivery gauge must read for each size welding tip in order to deliver the desired number of liters per minute to the patient.

Pounds pressure shown on delivery gauge.	Liters of oxygen delivered through welding tips.*				
	No. 1.	No. 2.	No. 3.	No. 4.	No. 5.
2	2	2.25	3.25	3.75	4
3	3	3.5	5	5	6
4	3.75	4.25	6	6	7
5	4	5	6.75	7.5	8
6	4.5	5.5	7.75	8	9
7	5.25	6	9	9	10
8	5.75	6.5	9.75	10	11

* I am very grateful to my former technician, Mr. Oscar Ugi, who derived these figures for me.

as satisfactory as and cheaper than so-called "medical" oxygen. The larger the tank the cheaper the unit of oxygen; the "large" 244 cubic foot tank will deliver 6905 liters of gas—enough for nineteen hours at 6 liters per minute. The apparatus in use in hospitals, and available on rental for use in the home in large cities, has pressure and flow gauges and conducts the oxygen through a humidifier en route to the nasal catheter. In the accompanying diagram and table I have sought to indicate how the ordinary oxyacetylene welding outfit (available in practically every auto repair shop throughout the country) may be converted very quickly into a satisfactory machine for the regulated delivery of oxygen to a patient. One should be very careful to keep oil of any sort away from all parts of such an apparatus.

Nursing Measures

The patient should be put to bed in a well-ventilated room and the use of the bedpan and urinal should be enforced of course. But having thus conserved the patient's strength it is doubtfully advisable to waste it again by permitting him to move about very much in order to facilitate the percussion and auscultation of his back. If the mouth is kept clean the patient will be more comfortable than when it is dry and dirty and he will also eat and drink with more relish; possibly, too, the danger of superinfection may be lessened. The best way to keep the mouth clean is to wash it with alkaline aromatic solution N.F. and then apply a small amount of petrolatum to the tongue and cold cream to the lips. Some patients also enjoy having the nasal passages cleaned out with a spray (see under Common Cold). The daily, quietly given, tepid sponge bath also contributes to the comfort of most individuals, but the omission of this sacred nursing ritual may be highly advisable on the worst days in the rare patient who has not responded well to one of the specific agents. As a matter of fact the sole reason for giving this bath is to cleanse and refresh the patient. If it tires and irritates him, as is very often the case when it is combined with a bustling bed-changing bout, why persist in it? No one has yet died from lying in bed for a few days without a bath or a stem-to-stern change of linens. Nowadays the initiation of disturbances of the nervous system through hyperpyrexia is very rarely seen, but when it is encountered the antipyretic drugs will control it much more safely than rigorous cold bathing procedures. I like very much Hall's (1936) reminding us of the old soldier's notice, pinned on the bed, "Too sick to be nussed today."

And when the corner has been turned? Two weeks in bed after the temperature is permanently normal, and a very gradual resumption of accustomed activities. I am aware that the new specific agents are "getting 'em out earlier," but I still think that a bit of a coddling period, particularly for those in or past middle age, is highly desirable after even the most fleeting bout of pneumonia.

Dietetics, Fluid and Chloride Administration

The course of an attack of pneumonia from diagnosis to defervescence or crisis being usually only a few days, there is no need to worry if the patient's total caloric intake falls somewhat below the normal. The chief concern should be that he is not given large quantities of food at the usual long intervals but instead is offered small amounts frequently. Most individuals lose completely their desire for solids but are very thirsty; they likewise sometimes prefer salted to plain water. This latter is considered fortunate since it has been

shown that the disease is often characterized by a considerable diminution in plasma chlorides, which would make the administration of sodium chloride theoretically advisable. Haden supplemented the food chloride by 6 to 24 Gm. salt daily, Sunderman, 15 to 30 Gm. It is highly desirable that as much of the patient's fluid intake as possible be taken in the form of fruit juices (orange, lemon, pineapple, grape, or grapefruit); flavoring these juices with milk sugar (lactose) or with dextrose instead of ordinary sugar (sucrose) is of advantage since additional calories can thus be added without too much sweetening. The following mixture (which I present as a formula) enabled Wilder and Drake to give chlorides, fruit juice, dextrose and water all in one drink:

Sodium chloride	1 Gm.
Dextrose	30 Gm.
Orange juice	200 cc.
Water	400 cc.

In the dietary outline which follows, the patient will obtain 50 Gm. of protein and 1800 or more calories, the latter depending upon what additional amount of fruit juice (or of the above mixture, preferably) he will care to take:

8 A.M. Fruit juice and cooked or packaged cereal with sugar and cream.
10 A.M. A glass of milk or buttermilk.
12 M. Fruit juice. A glass of milk or buttermilk. Soup made one half of strained vegetables, one fourth of milk and one fourth of cream.
3 P.M. Fruit juice. A glass of milk or buttermilk. A soft-boiled egg. (Or the milk and egg may be substituted by eggnog.)
6 P.M. Fruit juice. Milk and egg (if eggnog was taken at 3 P.M.) or eggnog (if milk and egg was previously taken).
8 P.M. A glass of milk or buttermilk.

Fruit juice, preferably prepared as in the chloride and dextrose formula, may be given several times during the night; it should be presented with some persuasion at least twice if the patient is awake. The patient is not to feed himself but is to use a glass tube for the liquids and the semisolids are to be spoonfed by the nurse. The subsequent return to the normal diet should be made by adding buttered toast and small servings of pureed vegetables, chicken, or red meat and potato to the above diet.

Symptomatic Treatment

Cough.—Though this is a beneficent measure, designed to rid the bronchi of foreign material which is choking them, it is sometimes excessive. Whenever cough is in the least degree exhausting the patient, attempt should be made to control it by such measures as have been described in the discussion of the common cold (see Index).

Pain.—The pain in the side is often satisfactorily controlled by judicious employment of adhesive plaster and a hot water bag; occasionally an ice-bag will give more relief but it should probably not be applied more than two hours consecutively. If the pain is very severe and causing considerable restlessness, only the opiates will give relief. Codeine, 1 grain (0.06 Gm.), may suffice; if not, morphine, $\frac{1}{8}$ to $\frac{1}{4}$ grain (0.008–0.015 Gm.), or dilaudid, 1/48 to 1/32 grain (0.0013–0.002 Gm.), may be given but the single dose perhaps had best not be repeated because of the possibility of increasing abdominal distention and decreasing pulmonary aeration. Sometimes also the patient becomes quite ill, even to the point of vomiting several times, a few hours after taking morphine,

perhaps more rarely after dilaudid. Some men feel that opiates should never be employed in pneumonia; the controversy is a very old one.

Diathermy sometimes induces great relief, and it is now the consensus that it has no effect other than that; Reimann (1939) said that in his experience a hot sandbag or water bottle provides just as much comfort at much less cost. Schnur (1939) sought to relieve pleural pain by local injection of procaine (novocaine), infiltrating 5 to 10 cc. of 2 per cent solution intracutaneously, subcutaneously and into the region of the pleura, most of it being injected deeply; immediate relief was obtained in all 32 cases and in 21 of them the relief was permanent. Artificial pneumothorax will also relieve pain but of course such a radical measure is rarely resorted to nowadays.

Restlessness and Delirium.—Restlessness and sleeplessness must be overcome since peace of mind and body are of considerable importance to the patient. Certainly no one can cavil at the statement that it is well to try a milder sedative before resorting to an opiate in order to secure bodily quiet. Delirium may appear very suddenly, even in a patient who has not been previously restless, and cause such violent exertion as to induce sudden death. Bullowa (1933) reported the satisfactory use of avertin in these cases, 60 mg. (1 grain) per kilogram (2.2 pounds) by rectum. When the patient was very violent and rejected much of the drug he used a barbiturate in addition—0.005 Gm. (1/12 grain) of dial-with-urethane per kilogram (2.2 pounds), intramuscularly or intravenously. The study of King and Moersch (1941) indicated that there is no danger in using the barbiturates in ordinary sedative dosage when the sulfonamides are being employed.

Tympanites.—Distention of the abdomen with gas is a symptom which is distressing and serious for it oftentimes adds to the respiratory embarrassment. Fortunately, in these days of specific therapy, it does not occur nearly so frequently as formerly. It is best treated by prevention; that is to say, by cleaning out the lower intestinal tract by a 1 per cent sodium bicarbonate enema as soon as the case comes under observation. In the opinion of many men this enema should be repeated at least every twenty-four hours, a rectal tube being used during the interim; others give ½ to 1 ounce (15 to 30 cc.) of liquid petrolatum every night and an enema only if needed because of distention. When distention is severe and persistent, turpentine stupes may be employed as in the following method.

First place a blanket under the patient in such manner that it can be drawn across the abdomen in "double-breasted" fashion. Anoint the abdomen with petrolatum. Then spread a Turkish towel over a small pan and place in the center of it another Turkish towel folded to the size of the abdomen. Now pour over this second towel boiling water, to which has been added 1 teaspoonful of turpentine to the quart, take up the two ends of the first towel, and quickly wring the stupe nearly dry by twisting these ends in opposite directions. Then remove this stupe, which is so hot that you can only hold it by rapidly shifting hands, from the wringing towel and place it upon the abdomen—and lift and replace, lift and replace, until the patient can bear the heat; then draw a layer of the blanket tightly across the abdomen from each side—and you have done it! The stupes must be applied every five minutes until relief is obtained, and in addition ½ to 1 cc. of pituitrin or pitressin may be given every twenty minutes for 2 or 3 doses.

The following carminative enemas may sometimes be useful: (1) ½ to 1 drachm (2–4 cc.) of turpentine, emulsified by beating with the white of an

egg, and added to a quart of water. (2) One to 3 drachms (4–12 cc.) of the emulsion of asafetida added to a quart of water; this latter preparation is esthetically very objectionable.

When dilatation of the stomach occurs the situation is indeed serious, though some men attempt to introduce a Levine tube or to employ the Wangensteen suction apparatus.

Circulatory Disturbances.—In many cases of pneumonia of moderate severity the pulse is no more rapid throughout than is consonant with the elevation of temperature. Also it not infrequently occurs in fatal cases that the failure seems to be entirely respiratory, pulse rate and force remaining quite good almost to the end. Again, we have to date no blood pressure studies which can be accepted as proof positive that early primary circulatory failure is *typical* of this disease. However, it is undeniably true that there is some degree of circulatory failure in most cases and that in many fatal instances the death seems to be primarily a circulatory one. We now know definitely that this failure is a peripheral circulatory one, though the mechanism of the vasodilation is not yet understood. Therefore, since it is peripheral vascular relaxation rather than heart failure with which we have to deal the situation is a very serious one indeed, for we have no drugs that are really satisfactory aids in such a situation. The Cornell and Rockefeller Institute groups conclusively showed many years ago that digitalis is not indicated; indeed, should auricular fibrillation supervene and necessitate the use of the drug it should be employed in dosage considerably lower than would routinely be used in such cases. Caffeine, metrazol, coramine, strychnine? They have all been tried and without much success. Eggleston (1941) considered adrenalin to be contraindicated. Rich (1944), and others before him, suggested that such circulatory failure as occurs in pneumonia might be due to adrenal insufficiency; indeed, Perla and Marmorston (1940) felt that satisfactory results were obtained by the use of cortin together with salts and excess fluid by mouth in 17 cases of pneumonia, but in these days of chemotherapy the opportunity for an extensive trial of this type of treatment is not likely to present itself.

Blood Concentration.—(a) *Venesection.*—In the days before the institution of chemotherapy, Underhill and Ringer studied a series of 43 cases of influenzal pneumonia from the standpoint of blood concentration, and were able to show a distinct relationship between the gravity of a given case and the extent of the abnormal concentration of the blood. Upon theoretical grounds they advocated the withdrawal of blood by venesection and the introduction of fluid into the body but were unable to carry out the treatment in many cases. It may be surprising to some to learn that a definite and logical basis exists for the letting of blood in pneumonia, a procedure which was at once the darling of our forefathers' hearts and the object of their greatest therapeutic abuse. A number of independent investigations, in pointing out the reactive leukocytosis, the coagulation changes, the hyperglycemia and the mobilization of antibodies, indicate that it may be considered as a form of protein therapy. Also, Petersen and Levinson, in reviewing the work of Lord and Nye and others, by which it was shown that a ferment-antiferment balance exists in the pneumonic exudate, reasoned that following venesection there may occur an alteration in this balance by reason of the withdrawal of some of the antiferment when fluid is rushed from the tissues into the vascular bed. To understand the logic of this it must be borne in mind that the ferments which are looked upon as overcoming the organisms are believed to be shed by the dying leukocytes at the

focus of the infection. Of course nowadays the indications for venesection rarely arise, but Conner (1941) felt that in some instances of pulmonary edema occurring early in the disease it may be justifiably resorted to; Eggleston (1941) agreed.

(b) *Dextrose.*—Since there is no reason to restrict fluids because the sulfonamides are being given, intravenous infusions of dextrose solution are holding their own very well in the new chemotherapeutic era. The most obvious advantage of dextrose therapy of course is that, while supplying fluids, it also makes available in a short time a large quantity of food material which does not have to undergo preliminary digestive processes.

Pulmonary Edema.—This is often a terminal event and nothing can be done. Sometimes, however, it occurs early in the attack. Venesection (see above) may be performed in these cases or one may give concentrated dextrose solution, as recommended by Bullowa some years ago: 100 to 150 cc. of 50 per cent dextrose solution intravenously at intervals of several hours, attempting to force the lungs to give up their fluids in order to dilute this concentrated solution. One may attempt to overcome excessive loss of fluid into the urine by giving insulin to help metabolize the dextrose; a little less than 1 unit for each 2 Gm. of dextrose, subcutaneously at the close of the intravenous injection. Barach (1942) felt that the administration of oxygen under positive pressure is indicated in some cases of pulmonary edema in pneumonia because the application of this positive pressure to the external capillary wall opposes the internal hydrostatic pressure in the capillary and thus tends to prevent the oozing outward of serum; but he stated that when pulmonary edema takes place in the presence of peripheral circulatory failure this positive pressure therapy is contraindicated for the reason that it has a retarding effect on the entrance of blood into the right heart.

Anemia and Hypoproteinemia.—Armstrong *et al.* (1945) reported two cases in which severe and progressive anemia and hypoproteinemia required the administration of large amounts of whole blood and plasma in order to save life after apparent bacteriologic arrest had been obtained through the use of penicillin. It is possible that cases of this sort will be seen with increasing frequency since we now have both the sulfonamides and penicillin to control severe infections which would otherwise be rapidly fatal.

PROPHYLAXIS

Vaccines made from killed pneumococci or from pneumococcus polysaccharides have been tried as prophylactic agents in institutions, particularly those harboring the aged and the feeble minded, but the findings are by no means convincingly in favor of their present employment. The papers of Kaufman (1941) and of Siegel and Muckenfuss (1941) will lead the interested reader into the literature. Of course the employment of the sulfonamides in upper respiratory tract infections before the pneumonic process becomes fully demonstrable is in itself a type of prophylaxis, but there is little to say about this sort of thing except that it is being very much done and probably has contributed considerably toward the decline in the incidence of pneumonia in recent years.

PNEUMONIA (ATYPICAL)

Primary atypical pneumonia of unknown etiology, frequently referred to also as "virus pneumonia," has been recognized only in recent times but is a matter of increasing concern because, though essentially a benign disease, it greatly incapacitated large numbers of both soldiers and civilians during War II. A deluge of papers upon this subject has appeared in the literature, but I think that the classical study was that performed by Dingle and his associates, acting as a committee to study the matter for the Office of the Surgeon General, and reported in May, 1944. In contradistinction to influenza and to pneumococcal pneumonia, the syndrome is characterized by gradual onset, mild symptoms referable to the upper respiratory tract, distressing cough, moderately severe constitutional reactions and a marked disparity between the early radiographic and the late physical findings in the chest. In most instances the patient has been suffering from an upper respiratory infection for days or weeks before he is sufficiently incapacitated to seek medical aid; the physician then finds an incapacitating malaise but rarely great prostration, chilliness often but true chills rather rarely, fever which is usually not very high, headache especially of a frontal type and often very severe, chest pains, and practically always a dry very distressing paroxysmal cough which later becomes productive but rarely purulent or frankly bloody or indeed even rusty. In an outbreak of 1862 cases at one of the Army posts, van Ravenswaay *et al.* (1944) were able to make careful observations on 297 consecutive cases and found that, while the initial physical findings were often confusing, the most helpful localizing symptom was the presence of râles which varied in character but most typically were dry and crackling and occurred in showers near the end of inspiration and could often be brought out by coughing when not otherwise present. In the rather characteristic radiographic picture usually presented early in the course of the illness by the majority of patients, the first change to be noted, according to Dingle *et al.* (1944), is an increase in the size of the hilar shadow, unilaterally or bilaterally. Perihilar infiltration becomes increasingly apparent in subsequent films and the shadow then extends toward the periphery in the shape of a fan or wedge, usually fading into the normal lung parenchyma but occasionally extending to the periphery. The infiltration is rarely of sufficient density to resemble that of pneumococcal pneumonia, and the process often appears confined to a local area and may spread within a lobe or to an adjoining lobe, but scattered discrete lesions throughout the lung fields are usually not observed. Neither sputum examinations nor blood cultures offer diagnostic aid, and the white and differential blood counts are not very helpful; Meyer and Thewlis (1944) recorded the following findings in 50 cases: the leukocyte count was usually normal, the neutrophils and monocytes increased, the lymphocytes decreased, and in about one fourth of the cases there was eosinophilia after the disease was somewhat advanced. The cold agglutination reaction has been studied by several workers, but in their review of these investigations together with their own, Streeter *et al.* (1944) stated the opinion that this laboratory procedure is not of definite diagnostic value in the individual patient. How much diagnostic aid is to be obtained from the discovery of Thomas *et al.* (1943), that serums of patients convalescent from atypical pneumonia frequently agglutinate an indifferent streptococcus, labeled No. 344, is yet to be determined. Van Ravenswaay *et al.* (1944) found that in the acute stage of the disease sedimentation rate is invariably elevated,

ranging from 20 to 40 mm. per hour, and that it returns gradually to normal as the patient improves; they felt that by the routine use of sedimentation tests it was possible to follow the progress of the cases as satisfactorily as by the routine use of periodic chest plates. Serious complications occur very rarely in atypical pneumonia and in most outbreaks the death rate has been extremely low; in the 1862 cases of van Ravenswaay *et al.* mortality was only 0.26 per cent even when they included three cases in which death very probably should not have been attributed to the pneumonia; in the series of 480 cases reported by Higley *et al.* (1944), complications of various types were found in 43 per cent but only 3 patients died because of complications. The febrile course in a case of average severity usually does not extend beyond a week, but there are not infrequently recurrences, or perhaps more correctly reactivations, for the pulmonary process seems to be of a relatively chronic nature, and therefore the period of convalescence is usually protracted. In the small number of fatal cases which have been investigated, the findings have been principally those of a patchy, hemorrhagic, interstitial bronchopneumonia associated with acute bronchitis or bronchiolitis; but Needles and Gilbert (1944), in reporting one of the autopsies, pointed out what they considered to be the striking similarity of the anatomic changes in this disease to those reported during the pandemic of influenza in 1918 and 1919.

In a few cases of apparently characteristic atypical pneumonia the following diagnoses have ultimately been made: influenza of either the A or B type associated with a staphylococcal or streptococcal infection, lymphocytic choriomeningitis, psittacosis, ornithosis, feline virus pneumonia, Q fever, coccidioidomycosis, pulmonary moniliasis, and finally bacterial pneumonia and pulmonary tuberculosis. But in the vast majority of instances the entity has not been identifiable with any of these diseases and it has to be accepted as a distinctive if not precisely new malady of cause unknown. There are many indications that it is a virus disease but this fact is not yet definitely established, though the results of an experiment by the U. S. Army Commission on Acute Respiratory Diseases, reported in early 1945, demonstrated that bacteria-free filtrates, presumably containing a virus, can induce atypical pneumonia in man. The incubation period has been said to range from two to twenty-one days or more, which means very probably that there is some epidemiologic factor which has not as yet been taken into account; indeed there are indications that many inapparent infections occur during an epidemic period of this disease and that perhaps many of the so-called "colds" prevalent at such times are really mild cases of atypical pneumonia. During an epidemic all age groups from childhood to advanced age, regardless of sex and race, seem to be susceptible.

THERAPY

In the present state of our knowledge the treatment is obliged to remain expectant and symptomatic since none of the specific chemotherapeutic agents have been successfully employed. Many observers have found the sulfonamides ineffective, and in fact Dingle *et al.* (1944) felt that their patients were more uncomfortable when receiving these drugs. Keefer *et al.* (1943), and Lyons (1943), reported the unsuccessful use of penicillin. It is probably well not to employ the salicylates because of the sweating manifested by many of these patients. Roentgen therapy was reported as having been very successfully employed by Correl and Cowan (1943), but one would like to see more

than a single report before forming an opinion. Solomon (1944) obtained good results with convalescent serum and pooled normal adult serum and felt that this sort of treatment deserves further study. In an attempt to determine the optimum period of bed rest which should be enforced, van Ravenswaay *et al.* (1944) made a controlled study of 384 cases divided into two groups; the members of one group were allowed to become ambulatory if they chose after they had been free from fever for four days, while those in the other group were required to stay in bed for an additional ten days, the total of enforced bed rest after becoming afebrile for this latter group being fourteen days. In the group treated by prolonged bed rest the percentage of recurrences was 2.6 and in the other group it was 23.3; members of the "bed rest" group were hospitalized only for 33.5 days as compared to 41.5 days for those in the "ambulatory" group. This study would seem to leave no doubt of the advisability of an enforced period of bed rest of two weeks after disappearance of fever in all cases. These observers also found that it was unnecessary to wait until x-ray and physical findings had completely cleared before beginning physical reconditioning in patients who had been afebrile for fourteen days. Kay (1945), however, would have bed rest continued until all evidences of pulmonary infection have been cleared for he had seen some cases of bronchiectasis following a protracted course of atypical pneumonia.

POLIOMYELITIS

(*Acute Anterior Poliomyelitis, Infantile Paralysis*)

Poliomyelitis is an acute infectious disease which typically attacks young children, those under six years of age being in the most susceptible group though infants under six months are very infrequently attacked; adult cases are reported less rarely now than formerly. The causative organism, a filtrable virus, seems to go through avirulent and virulent periods, during both of which many mild, so-called "abortive," cases occur in which there is little or no paralysis, though immunity is conferred by such an attack; during the more virulent periods the disease tends to become epidemic—pandemic, too, at least to the extent that a large number of local epidemics may occur at about the same time scattered throughout the world. Several observers have thought that there was some evidence of connection between the harvest time for perishable fruits and vegetables in various parts of the world and the incidence of infection in epidemics there, but Toomey *et al.* (1943) failed to recover the virus from fruit washings. Of course the fact must not be overlooked that such seasonal periods may merely coincide with the height of activity of some hitherto unsuspected or at least unconvicted insect vector (recent work redirects attention to the common housefly, the blowfly and the greenbottle fly). Moore and Kessel (1943) presented a hypothesis that poliomyelitis is primarily a disease of extracentral tissues with the seasonal incidence of paralytic complications due to variations in the physiologic resistance of the host. There has been some speculation on the possibility that one or several of the lower animals may act as the great reservoir for the virus, the most positive evidence in this direction being Jungeblut and Dalldorf's demonstration of the virus in the body of a recently dead gray house mouse discovered in the home

of a fatal human case. At least one fact is certainly established, namely, that the virus is often recoverable from the stools of patients and of healthy contacts and from the sewage in the vicinity of isolation hospitals; Kessel and Moore (1945) also recovered the virus from both tonsils and stools of noncontacts during an interepidemic period. Maxcy (1943), however, maintained that there is not sufficient evidence to prove the water-borne nature of the spread of the disease. There is nevertheless a growing conviction in recent years that infection with poliomyelitis virus is usually by way of the alimentary tract, the actual passage into the tissues being through the pharyngeal mucosa, the mucosa of the intestinal tract, or both, with subsequent central spread along the axis-cylinders of nonmedullated nerves. However, the studies of Howe *et al.* (1944) at Johns Hopkins, and Faber *et al.* (1944) at Stanford University, in the first of which nasopharyngeal washings from active cases were found to produce a disease when inoculated intracerebrally in monkeys, and in the second of which monkeys caused to inhale an atmosphere containing the virus suspension delivered as a fine spray came down with the disease, certainly redirected attention towards the possibility of droplet infection or contaminated dust transmission. Since monkeys can be infected both by the ingestive and inhalational routes, the main problem awaiting solution would seem to be the determination of which is the chief or sole route responsible for the infection of man. In recent times the white mouse, the cotton rat and the Syrian hamster have been added to the monkey as experimental animals which may be satisfactorily used in the study of the disease.

The early symptoms of poliomyelitis are "cold in the head," cough, more or less vomiting and diarrhea, fever and extreme irritability with coincident malaise and restlessness. Reluctance to lower the chin, and also the assumption of a peculiar position in the bed, may be seen at this stage. Then, in severe cases, and either with or without a remission of several hours to several days, the more severe headache and typical flaccid paralysis of some portion of the body appear. The course is now usually afebrile, but the child often experiences so much pain on being moved that it frequently manifests excessive apprehension when any person approaches the bed. Three types of respiratory difficulty are distinguishable: the type due to involvement of the respiratory muscles, that due to involvement of the respiratory center and usually denominated "bulbar paralysis," and that resulting from inability to swallow saliva and mucus. It is felt by some but not all observers that the higher the cell count in the spinal fluid, the more severe the attack; in the prodromal stage the fluid is clear but under increasing pressure. Rosin *et al.* (1944) stated, on the basis of a study of 96 patients, that in the individual case there is no correlation between the severity of the disease and the sedimentation rate or white blood count. In 7 of 9 autopsied cases Peale and Lucchesi (1943) found myocarditis of some degree in addition to toxic and degenerative changes in the cardiac muscle. Poynton (1943) reported an unusual type of outbreak of poliomyelitis in which arthritis often appeared as a complication.

It seems to me that in recent years we have learned much about poliomyelitis from Elizabeth Kenny and that she in turn has learned much from us during her sojourn here in America. Indeed it is at once most fortunate for her and for the medical world that after her wandering she had the opportunity to settle down at the University of Minnesota among a group of men who, admittedly skeptical when not actually hostile in the beginning, had the gift of the open mind and the ability to humble themselves and to learn. Not being

one given to habitual overenthusiasm, I have neither the wish nor the desire to sing a paean of praise for the Kenny concept, but it seems to me that those who oppose this new viewpoint are on far less substantial ground than is the Kenny group when they object because money is being spent to investigate a new method of physical therapy, as did McCarroll (1942), or when they take the attitude, which it seems to me was done by the committee of which Ghormley (1944) was the chairman, that anything of value stressed by Kenny was known to and has been practiced consistently by pediatricians for many years, all the rest being simply untrue. The older concept, that which I should like to call "orthodox" were it not that to do so would give offense to some of my orthopedic friends, holds that the muscle weakness or actual flaccid paralysis in the acute stage is due to a toxic (viral), edematous, or perhaps actual hyperplastic assault upon the anterior horn cells in the cord; that pain is the result of meningeal irritation; that deformities are caused by the unopposed pull of muscles opposite those that are weak or paralyzed; that such deformities are to be prevented by judicious splinting supplemented by certain physiotherapeutic measures; and that the amount of residual paralysis in any case is dependent upon the amount of destruction in the central nervous system, the latter varying tremendously in different epidemics. Now in opposition to this the Kenny group offers something entirely new, or if not entirely new something that has at least been so infused with life by its chief proponent, and so worked over and systematized by those whom she has won to her support in Minneapolis, as to have acquired sufficient impetus to require that it be reckoned with. It is undoubtedly true that Kenny is today giving a place of utmost importance to things she hardly mentioned a very few years ago; it is also a fact that even in her latest book, that written by Pohl and Kenny (1943), not all portions are presented in a fashion so likely to satisfy as they are to interest; it is also true that the promotional and publicity methods pursued by Kenny's sponsors have often made one wish that no part of this at all were being done in the name of medicine; it is also true, or so the rumor runs, that Miss Kenny herself, like many another intrepid crusader, has not always turned upon her cavilling opponents the weapon of a candid and tactful smile. But all of this it seems to me may be tolerated, if not precisely condoned and certainly not applauded, provided the Kenny group has a concept of poliomyelitis to offer which will drag this disease up out of the rut in which it has lain for many years; and an additional proviso I would make: this viewpoint must meet rationality at a sufficient number of points to provide experimental scientists an opportunity to attack and destroy or confirm it. It seems to me that both of these desiderata have been at least partially met. The concept of the Kenny group does not deny the long established pathologic attack upon the cells in the anterior horns of the cord, nor would it, I imagine, concern itself with Carey's (1943) interesting experimental finding of possible preceding or accompanying morphologic changes in the peripheral motor nerve endings and muscle fibers, but it does hold that many of the difficulties under which the stricken patient labors are primarily symptoms engendered by muscle spasm, muscle incoordination and mental alienation.

Muscle spasm: The action of the virus on the neurons may be in some instances totally destructive so that there is a resultant permanent loss of function; but according to the Kenny concept, if I understand and can interpret it correctly, the extent of the damage is often only partial and temporary and

one of its effects is the production somehow of widespread muscular spasm. This muscle spasm, which is most usual in the muscles of the back and neck, the gastrocnemius muscles, pectoral muscles, muscles of respiration, quadriceps muscles and the biceps of the arms, is felt to be principally responsible for the apparent flaccid paralysis, since it is argued that the affected muscle is not actually that one which seems to be paralyzed but its opponent which is in a state of hypertonus. This hypertonus will frequently cause deformity, as in the well known "foot drop" caused by spasm of the posterior calf muscles, or an elevated shoulder from spasm in the upper trapezius which may ultimately be the cause of a scoliosis, or spasm of one quadratus lumborum resulting in a unilateral lordosis with pelvic tilt and apparent leg shortening. Muscles in spasm are usually both painful and tender and it is felt that continuance of the spasm for a long period of time results in irreversible contracture due to ultimate fibrous degeneration. Spasm occurs both in muscles which can and cannot be contracted voluntarily, *i.e.*, there seems to be no direct relation between spasm and motor paralysis. Of the several attempts which have been made to study this spasm on an experimental basis, that of Kabat and Knapp (1944) is of special interest. These workers found that the spasm is apparently due to an increased discharge of motor nerve impulses from the spinal cord to the affected muscles, since elimination of this excessive discharge by spinal anesthesia or by drug block at the myoneural junction was effective in relaxing the spasm in the cases in which these methods were employed. Furthermore, it was found that the pathologic involvement of the anterior horn cells is probably not the basis of muscle spasm, for (*a*) studies of the chronaxie of poliomyelitis muscles in spasm showed that some did but others did not give any evidence of denervation; (*b*) muscle spasm similar to that observed in clinical poliomyelitis was produced in dogs by temporary arrest of the circulation of the spinal cord, and subsequent postmortem examination of the spinal cords in these animals revealed only lesions of the small internuncial neurons which lie in the region between the anterior and the posterior horn; (*c*) since these internuncial neurons form in a sense a switchboard mechanism controlling the motor neurons, it was felt to be a reasonable hypothesis that a lesion of these internuncial neurons might produce a localized muscle spasm on the basis of release of anterior horn cells from inhibition; (*d*) in going over sections of the spinal cord from 68 patients who had died in the acute stage of poliomyelitis it was found that in 26 instances the lesions were predominantly in internuncial neurons with relative sparing of anterior horn cells. The clinical observation that patients with mild poliomyelitis have muscle spasm without paralysis might be taken to indicate that in them there was only internuncial and not primary anterior neuron involvement. According to this hypothesis it would be only the anterior horn cell lesion which results in motor denervations with ultimate muscle atrophy. In the milder cases spasm may subside spontaneously, but often when untreated and severe it persists for months or years, occasionally indeed even when actively treated from the very beginning of the acute stage.

Mental alienation: It is a long established fact that the movement of a joint is accomplished by the contraction of a muscle or set of muscles while at the same time its opponents are relaxed in order to effect the movement; therefore in poliomyelitis the explanation for the apparent paralysis of a muscle which later recovery shows not to have been paralyzed would be that it was kept in a state of flaccidity through participation in the normal reflex, *i.e.*,

it would be relaxed because its opponent was in a state of spasmodic contraction. The Kenny group holds that a muscle relaxed in this way is only apparently but not actually paralyzed since its flaccidity is really brought about through the performance of its normal function of relaxing when called upon to do so; it is referred to as "mentally alienated" because in a sense the patient does not know quite how to send an impulse down to effect contraction in it while its opponent is in a spasm which calls for its relaxation. Bennett (1943) and others have pointed out that what is here called mental alienation is by no means a new medical entity since the loss of voluntary contraction in muscle groups following surgical procedures about joints is not infrequently seen.

Muscle incoordination: This third leg of the tripod of the Kenny concept should really not startle anyone because, as pointed out by Watkins (1943), it is generally recognized to occur whenever there is attempted motion with partially paralyzed muscles around a joint and also when the joint is immobilized. It consists simply in the substitution of accessory muscles, or even antagonist muscles, for the proper prime movers of a joint when the afflicted individual attempts to regain voluntary control; sometimes even individual muscles contract improperly in sections rather than through their full length. An example of this muscle incoordination would be the attempt of a patient to breathe with his sternocleidomastoids, his pectorals and even with the platysma in the skin of the neck when there is spasm of the intercostal muscles.

Poliomyelitis is a very ancient disease; it is thought to be represented on one of the stelae of the eighteenth dynasty (1580 B. C.) in Egypt. The first modern account of the predominating infantile type was that of Michael Underwood (1784), though many feel that there was some doubt about his cases and that Heine really established the disease as a clinical entity in 1840. Duchenne, in 1855, first pointed out the relationship of the lesions in the anterior horns of the cord to the paralysis. Negroes are thought to be much less susceptible than whites. The investigations of Hudson and Lennette (1938) indicated wide distribution of the virus throughout the world. Though the report of Mumford and Mohr (1944) regarding incidence in the tropical Pacific upset the notion that the clinical disease is rarely seen in the warmer climates, Simmons *et al.* (1944) stated that a true epidemic has never been described in the Netherlands Indies. Relapses and second attacks of poliomyelitis are of relatively rare occurrence. Fox and Sennett (1944), reviewing the literature and their own cases, felt there is strong evidence that pregnancy increases the susceptibility to poliomyelitis. However, infection in the mother does not seem to hamper delivery nor does the fetus seem ever to become infected. Casey's (1942) study of 36 instances in which the initial case in a neighborhood followed a single short visit to or from a prior victim of the disease, established an incubation period of five to thirty-five days with an average of twelve days. Aycock and Kessel (1943) seemed of the opinion that the period of greatest infectiousness is during the first three or four days of the acute attack.

THERAPY

There is no evidence that the Kenny treatment prevents or decreases or cures paralysis, indeed that is not its aim. I have also seen no evidence in the literature that anyone seriously believes that a patient can be saved in whom

there is overwhelming bulbar involvement. But the claim is made that in this type of treatment there is effected the most complete alleviation of the symptoms in the acute stage, and that it is more effective than the older type of treatment in the handling of respiratory embarrassment due to involvement of the muscles concerned in the respiratory act, and likewise in the prevention of serious residual disabilities. I shall not attempt to balance the statistics of one set of protagonists against those of the other for the reason that the only type of statistical study that can be of any really scientific value has not yet been performed, namely, the employment of the older type of treatment and the Kenny type of treatment in alternate cases in a very large series of patients in one place and during one epidemic. But I do believe that the declared observation of facts, however unsupported statistically, of Pohl (1942), Daly *et al.* (1942), Stimson (1942), Knapp (1942), Blount (1943), Krusen (1943), Bennett (1943), Watkins (1943), Snow (1944) and Stewart (1944) are allowable, some of these well-trained observers bearing witness in part and others *in toto* to the admissibility of the aforementioned claims. There are others who, in an excess of enthusiasm, have repeatedly declared that they have seen "absolutely no deformities" following employment of the Kenny method, which is unfortunate since it is known that some patients so treated do have flail extremities afterward and that some of them walk with a Trendelenburg limp, these things certainly being deformities. But Krusen (1943), who withheld judgment during a three-year period of close observation before he pronounced himself to be in support of the Kenny method, said that what he believed these over-zealous observers to mean was that they had seen no contractures, malignments, or spinal curvatures attributable to contractures following this treatment; and he said that he was willing to concur in such an observation. But the objections to the Kenny method in addition to those advanced from the "orthodox" standpoint by certain of the orthopedists are several: it is ritualistic, it can be properly instituted and carried through only by specially trained personnel and its employment is very expensive. But it seems to me that these are essentially only matters of the passing moment since if the Kenny contribution is really a fundamental one its simplification will logically pace its rationalization.

I can no more describe the Kenny treatment here than I can the older type of treatment since both require the employment of technics to be mastered only under guidance at the bedside. What follows therefore is a mere outline of the two types of treatment together with a statement of some other matters which require separate attention.

Kenny Method of Treatment

At once after the diagnosis is made in the acute stage the patient is placed at rest on a bed in which a soft blanket has replaced the sheet and boards have been introduced under the mattress to give a stiff firm surface. The attempt is made to maintain an awareness of muscle function by having the patient lie flat on the bed in either the supine or prone position with the arms along the side, the head in a natural position, and the feet at right angles to the legs in order to stimulate the proprioceptive senses by simulating the standing position. This latter achievement is accomplished by placing a board at the foot of the bed and inserting 4 inch blocks between it and the mattress, so that when the patient is lying supine his feet will be placed against the board and his heels will not be resting upon the bed surface but will be down in the

opening, and when he is lying on his face the toes will stick down into this opening. However, during such time as there is spasm of the calf muscles the attempt is not made to bring the feet at a right angle position to the legs by placing them against the board, for the reason that it is felt unwise to stretch muscles which are in spasm. Splints, sand-bags, or casts are not employed for immobilization, but in this early stage therapy is directed chiefly toward the reduction of spasm by the use of hot applications. Woolen packs made by cutting old blankets to proper size are immersed in boiling water at the bedside, twice rung through a tight wringer, quickly applied to the involved area, and then covered with oiled silk and dry flannel which is held in place with pins or binders if necessary. All the muscle areas in spasm must be accurately covered by these packs, but the joints are left free so that the patient will not have any sense of immobilization of the limbs. Exceptions to the latter rule must of course be made when the muscle itself covers a joint, as for example the deltoid over the shoulder joint, and the joints of the hands and feet are necessarily covered because of the small area involved. The packs are usually renewed every two hours throughout twelve hours of the day, but when spasm is unusually severe or threatening the life of the patient they may be applied as frequently as every fifteen minutes, and in some instances they are applied every two hours or even oftener around the clock. Since it is felt by the Kenny group that spasm may be aggravated by frequent examination or rough handling, no active or passive movements or muscle testing are allowed during this acute stage and it is felt to be obligatory that the nursing be done with extreme gentleness. Spasm is said to be relieved in a few days to a week in some cases but in others some muscles may be required to be treated with hot packs for months. All muscle spasm, not only that involving the muscles of locomotion and the prehensile and postural movements, is attacked by the application of these hot packs. For example, respiratory embarrassment due to spasm of the intercostals and pectorals or of the diaphragm is vigorously combated by application of the packs to these areas, packs are applied around the neck to combat disturbances of swallowing, and to the abdominal and lower back muscles in the attempt to overcome difficulties in emptying the bowel and bladder. Snow (1944) emphasized the point that packing of an area should not be discontinued until it was certain that the need no longer existed, since he found it very discouraging to patients to have packing resumed after its discontinuance.

After spasm has been eliminated muscle reeducation is begun and is continued through the necessary number of weeks or months or even years until its goal is achieved, namely, to restore muscle power and balance in such wise that instead of limping and lurching movements there will result coordinated movements and a smooth rhythmic pattern of motion. To accomplish reeducation the most painstaking efforts are required to teach the patient to employ only the desired muscle or group of muscles while the opponents are relaxed and no other incoordinated contractions are permitted to occur. In short, the aim is to teach the use of the right muscle at the right time without the distracting effects of other unnecessary and undesirable muscular contractions. The patient is placed on a treatment table in the same natural position which he occupied during the period of acute spasm, he relaxes and fixes his attention solely upon the movement that is to be attempted. Usual practice seems to be for the technician to grasp the part firmly and to move it twice passively through whatever range is possible without producing pain.

Then the technician, having instructed the patient what is required of him by stroking the exact insertion of the muscle group to be trained and requesting him to attempt to achieve a mental consciousness of the contraction desired, assists him once through an active-passive movement of the part, and then calls upon him to perform the motion himself through concentration on the act. Should the patient's attempt result in bringing into play muscles other than the one to be trained, the attempted motion is stopped at once and the interloping muscles are put out of action either by instructing the patient to do so or by finger pressure against the muscle on the part of the technician. In the beginning, when any degree of visible or even palpable motion is achieved in the muscle upon which attention is being concentrated the movement is stopped so that the patient may be left with the sense of accomplishment. It is felt that at any session in which the patient is not fully cooperative or whenever he manifests fatigue the attempt must cease at once. If no trace of motion is achieved it is felt that the muscle may be stimulated through its tendon by placing the muscle on a slight stretch and then moving the joint backward and forward until the tendon can be followed along its course. Experience has confirmed Cole *et al.* (1942), who stated that if this latter procedure makes it possible to follow the course of the tendon from its insertion to the belly of the muscle, that muscle can eventually be returned to a functional state; "loss of tendon" is according to this viewpoint indicative of complete loss of muscular tone and considered to indicate probable permanent and complete loss of function. Pool treatment and the process of reeducation under water are not practiced by the Kenny group principally for the reason that movements performed under water are felt to have no counterpart in useful human movements performed on dry land and therefore place the patient at a disadvantage when he is obliged to cope with the direct forces of gravity as affecting his everyday posture. However, baths of two sorts are employed during the reeducational phase, the bath often being given just preceding the reeducation exercises on the treatment table. These baths, the object of which is to help the patient retain consciousness of his body structures in the campaign against alienation and incoordination, consist either of a general warm bath, or, where there is sluggish circulation, the douching of the patient as he lies in the tub first with warm and then with cold water, these douches being succeeded by a warm immersion bath before the patient is removed to the treatment table. No reeducation procedures are of course carried out in the bath.

The Older Type of Treatment

Those who adhere to the older viewpoint regarding poliomyelitis believe that the most hopeful single item that has evolved out of all the world's deep study of the disease is recognition of the fact that, since involvement in the cord is "spotty," there is rarely complete paralysis and ultimate degeneration of the muscle groups involved. The meaning of this, to those who abjure Kenny and all her works and adhere to the orthopedic principles laid down by Lovett (1917) and stressed by the Kendalls (1938), is that if contractures are prevented by suitable immobilization during the acute stage of tenderness, and if thereafter muscle training is properly begun and indefatigably prosecuted, the chances for recovery without permanent crippling deformities are very good. The measures which an orthopedist of this "orthodox" group applies with the help of his physiotherapist assistants comprise principally the following:

(1) By the use of such pillows, sand-bags, splints, or other mechanical devices as are necessary the various parts of the body will be placed in physiologic rest at once, alterations in the positions of the parts being made when the extent of the paralysis has become established.

(2) Local circulation is maintained and pain is combated by the application of external heat in the form of hot wet packs or hot baths, if these can be given without disturbing the patient.

(3) When pain disappears massage is begun, with possibly immersion saline baths to obtain surface hyperemia, but without movement or manipulation of the affected parts even under water.

(4) There is gradual increase in force and duration of the massage followed by the introduction of passive movements.

(5) Active movement finally begins after careful analysis of the deterrent effects which gravity, friction and atmospheric pressure are likely to have on the movement. The advantages of under-water treatment are held to be: (*a*) The buoyancy of the water counteracts the influence of gravity and friction so that the sense of accomplishment cheers the patient. (*b*) The wide range of activity also diverts and is inspiriting during the protracted treatment. (*c*) Knowledge of body balance gained under water is helpful to the patient in adjusting himself to walking in braces later.

(6) When the maximum amount of recovery has been accomplished by muscle reeducative measures and the application of braces, operative surgery may be undertaken to accomplish transplantation of muscles and tendons and the eradication of unstable joints by bone fusion.

Combating Respiratory Difficulty

The Kenny group concedes, as expressed by Pohl and Kenny (1943), that when respiratory difficulty is due to actual paralysis of the respiratory muscles the use of the respirator would assist the patient in breathing. But they make the point very strongly that such cases of respiratory muscle paralysis occur very rarely and that in most instances the respiratory difficulty is the result of spasm of the intercostal muscles and is to be treated by hot packs as is any other spasm. The use of the respirator in this type of case is therefore opposed not only because it prevents relaxation of the muscles of respiration but because it interferes with the application of the hot fomentations. Pohl and Kenny (1943) said very plainly "the respirator is therefore of no use in the treatment of respiratory distress due to intercostal muscle spasm." They further stated that the respirator is contraindicated in a patient whose difficulty is due to spasm of the diaphragm because such a patient is already in a condition of what they called "literally drowning in air" and his chest expansion would only be increased by the respirator. It is admitted that relief of spasm of the respiratory muscles through hot packing is sometimes very difficult of accomplishment, but it is felt by the Kenny group that patients who die while receiving hot packs without the respirator would also die if treated by the respirator. This is probably the most vigorously opposed of all the pronouncements that have come out of Minneapolis, and even men who are very favorably inclined toward the Kenny treatment and have indeed adopted it practically *in toto* have in many instances refused to accept this dictum, for they stoutly support such a statement as that of Wesselhoeft (1943): "I have seen the respirator relieve too many patients with acute and serious temporary respiratory embarrassment of the spinal type—patients who have recovered

and walked out of this hospital to lead useful lives—to subscribe for one moment to the violent prejudice against the respirator emanating from the Kenny adherents." So the point is currently hotly controversial, but for my part I must say that I admire the Kenny group for their consistency since if their concept is not only new but true then of course hot packing for the relief of respiratory muscle spasm is the logically indicated therapy.

In the United States respirators of the Drinker and Emerson types, the popularly called "iron lung," are preferred, but in England much use has been made of the Bragg-Paul Pulsator, an air bag placed around the patient in the manner of a corset and rhythmically inflated and deflated by an electrically operated pump. The Pulsator has also been used to some extent in our country, but I believe the consensus here is that its effect, which is obtained by exaggerated expiration as the result of rhythmically-produced periods of positive pressure on the chest wall, is not as desirable as that of the other respirators which operate by means of rhythmically-produced periods of negative pressure.

Combating Bulbar Paralysis

When the vital centers in the medulla are affected the situation is often an extremely serious one but it is by no means always hopeless since many of these patients do recover. In this state there is a marked decrease in the rate of the respirations and they become shallow and irregular both in rhythm and in depth. In addition, pharyngeal and laryngeal paralysis make it impossible for the patient to swallow or to cough and the mucus is inspired and causes the "wet" type of respiratory failure, the ultimate event often being the development of a fatal pneumonitis.

Long before Kenny bounded upon the poliomyelitis stage it had been decided that the use of the *respirator* is contraindicated here, so upon this one point at least both the Kenny-ites and their opponents are in perfect accord. The reasons for this contraindication are two: first, when the respiratory center is involved the patient's breathing cannot be made to synchronize with the machine, and second, the respirator will cause the mucus to be more forcibly drawn down into the trachea whereas, as pointed out by Wesselhoeft (1943), the patient's own intuition prompts him to avoid this by shallow breathing. *Postural drainage*, which is accomplished by elevating the foot of the bed (as much as 15 to 20°) with the patient's head turned to one side, is perhaps the most helpful of all measures, though *suction* through a rubber catheter having several openings near its tip often gives great additional relief. *Atropine* is rarely as helpful in checking the secretions as might be expected; indeed, Wesselhoeft (1943) said it has sometimes been found to render the mucus more tenacious, more annoying to the patient and more difficult to remove.

Though Pohl and Kenny (1943) opposed *duodenal tube feeding* because in their belief it excites spasm, increases mucus and interferes with swallowing, it is nevertheless not infrequently resorted to in order to maintain nourishment in the patient. The Levine tube, which resembles a urethral catheter with openings on the side at the terminal end, comes in sizes 16, 14 and 10 French. It is about 45 inches long and is preferably passed through the nose. For use in such feeding, Miller (1939) mixed, ground and sieved the following ingredients, stored the mixture in six portions in the refrigerator and fed one portion every three hours during the day and every four hours during the night to a patient thirteen years old: 20 per cent cream, 100 cc.; milk, 1000 cc.; eggs, 6; 5 per cent vegetable, 180 Gm.; 10 per cent vegetable, 100 Gm.; cornstarch, 30

Gm.; orange juice, 150 cc.; Karo, 96 Gm.; a small amount of salt. This diet supplied something over 1800 calories per day and was satisfactory from the standpoint of mineral and vitamin content. Toomey (1944) warned against the use of *sulfonamides* which he seemed to think had produced an additive neurotoxic effect in these cases, nor had he found *penicillin* of much help in his experience. However, with regard to penicillin, Fox has told me that he felt it was of value when used by him during the epidemic in Milwaukee in 1944 in relatively small doses three times daily for the prevention of pneumonitis; this latter observer also feels that these patients should be treated as for *shock* (see Index).

Miscellaneous Measures

Neal (1941), whose experience in poliomyelitis has been vast, said that she had often found *spinal drainage* to be of value if there are signs of meningeal irritation, but she warned, of course, against its employment in cases of severe bulbar paralysis and in completely asthenic patients. In cases of edema of the brain, concentrated dextrose or sucrose solutions (see Index) may also be tried. Retan (1937) described a type of treatment resting upon the frequent intravenous injection of *hypotonic saline* solution combined with graduated spinal drainage, but Kramer *et al.* (1942) reported negative results with the employment of this method in experimental poliomyelitis in monkeys; the procedure is complex and has a number of contraindications, so a description here does not seem to be warranted. *Convalescent and adult serums* have had a long trial but have failed to make a place for themselves. In a series of 20 cases Kabat and Knapp (1943) employed *prostigmine* as adjunctive therapy in the Kenny type of treatment, the drug appearing to accelerate recovery in most of the cases through promoting a relaxation of muscle spasm and reducing incoordination, actions which these observers felt were apparently dependent upon alteration of function of synapses in the spinal cord, *i.e.*, the postulation of an entirely new kind of action for this drug. Prostigmine was given subcutaneously in the form of the methylsulfate and orally in the form of the bromide salt, the unpleasant parasympathetic symptoms induced being opposed by the concomitant employment of atropine sulfate. Dosages were as follows: for adults 1/40 to 1/30 grain (1.5–2 mg.) of prostigmine methylsulfate together with 1/100 grain (0.6 mg.) of atropine sulfate; for children of eight to thirteen years, 1/60 grain (1 mg.) of prostigmine with or without 1/200 grain (0.3 mg.) of atropine; for children of two to six years, 1/120 of a grain (0.5 mg.) of prostigmine without atropine. Oral administration was begun in most cases after initial injection of prostigmine but in some cases oral doses alone were used. For adults the usual dose was gradually built up to $\frac{3}{4}$ grain (45 mg.) of prostigmine bromide and 1/100 grain (0.6 mg.) of atropine sulfate (given simultaneously) three times a day. The children of twelve to fourteen years received $\frac{1}{2}$ grain (30 mg.) of prostigmine bromide and 1/200 grain (0.3 mg.) of atropine sulfate three times a day. Younger children were given $\frac{1}{4}$ grain (15 mg.) of prostigmine bromide two to five times a day without atropine. It was said that these doses usually did not cause toxic or unpleasant symptoms but that the balance of prostigmine and atropine had to be adjusted carefully to the individual patient to avoid such symptoms. I understand that prostigmine was very widely used in the epidemics during 1944, and the findings of Eveleth and Ryan (1944) on a small series of cases to some extent confirmed those of Kabat and Knapp, but a number of physicians have verbally reported to me results which were quite inconclusive.

PROPHYLAXIS

Hygienic Precautions.—The paucity of our knowledge of the mode of dissemination of this disease was indicated in the beginning of this article, so it therefore cannot be expected that any very exact directions can be set down here for precautions to be taken during an epidemic. Indeed we do not understand why, despite the recognized high incidence of multiple familial cases (the incidence was 9.29 per cent in 721 cases in the series of Swartout and Frank, 1944), the disease occurs in the main in a very spotty fashion, and the actual incidence of cases in any given area is very low even though the disease is at the time at one of its epidemic peaks in that area. Many departments of public health do the only thing that they can do, namely, proceed upon the assumption of contagiousness and institute rather rigid quarantine precautions during an epidemic. However, it has not yet been demonstrated that the closing of schools, theaters, bathing beaches and other gathering places, and the confining of children to their homes, as was attempted here in Milwaukee during our epidemic in 1944, has in any way altered the course of an epidemic. But these things probably do no harm, though it is certainly very interesting that, as pointed out by Ward and Melnick (1944), in the fall when schools open and chances for contact infection become greater among children epidemics of infantile paralysis fade away. These same observers said that there is not as yet enough evidence available to justify an opinion that the virus cannot survive treatment in a modern water purification plant. Since a history of overexertion is said often to precede an attack, many men feel it advisable to attempt to curtail children's physical activities during an epidemic.

Tonsillectomy.—It is the consensus among leading students of poliomyelitis that tonsillectomy predisposes to the severe bulbar form of the disease. In fact, Aycock (1944), who has been a leading student of this phase of the studies, has stated that since this operation is practically always elective as to time, changing the season when it is done so as not to coincide with the season of poliomyelitis prevalence is the one preventive measure that can be used with assurance in this disease.

Quarantine.—The White House Conference recommended an isolation period of three weeks from the onset of febrile symptoms, for the patient and other exposed children. Placarding was not recommended.

PSITTACOSIS

(*Ornithosis*)

This is an acute infectious disease of birds, easily transmitted to man. The birds in which the disease is so far known definitely to occur are the following: parrots, parrakeets, budgerigars, finches, canaries, pigeons, chickens, and at least one member of the petrel family. The disease, which is caused by a virus that is oftentimes harbored by apparently healthy birds, can be experimentally transmitted to some of the smaller rodents and to monkeys as well as to birds. The virus has been cultivated *in vitro*.

In man psittacosis occurs usually in house epidemics among persons handling infected birds, but it is also possible for direct transmission to occur from human to human, as was demonstrated in the Pittsburgh outbreak of 1934. Psittacosis has taken its toll of doctors, nurses and laboratory workers. The

two greatest outbreaks have been that in Paris in 1892 to 1895, in which there were 78 cases with 24 deaths, and the present pandemic in which, at the height in 1930, more than 500 cases were reported on the Continent, in England, North and South America, and the Hawaiian Islands. Small epidemics are still being reported, though with lessening frequency. Cases have been traced to infected birds in shipments from many countries; I believe that in the United States many of the cases have been traceable to birds from California, simply because the raising of pet birds has become a large industry in that state.

Children are notably less susceptible to the disease than adults. Mortality seems to average about 20 per cent, but the number of mild and unrecognized cases cannot be estimated, of course. There is one recorded instance of a person having a second attack of psittacosis. Though the incubation period is not as yet definitely established, it is believed to be between seven and fourteen days in most instances. The Meyer-Eddie modification of the serum complement-fixation test of Bedson is considered to be of great assistance in making the diagnosis.

In man the first sign is usually a chill with subsequent rise of temperature and a pulse rate that is not commensurate with the fever, also headache, backache, loss of appetite, white-coated tongue with red edges, abdominal distention; there may be vomiting and either diarrhea or constipation; sometimes, but not invariably, there is leukopenia. Upon this typhoid-like picture is engrafted a pneumonia which is atypical in that there are pronounced physical signs of pulmonary involvement often without much sputum or pain in the chest, though the cough may be severe. Albuminuria as well as nervous symptoms are often in evidence. The attack may run a course of many weeks, the pulmonary symptoms frequently continuing long after the temperature has subsided. Smadel (1943), and Favour (1943) and others, have pointed out that psittacosis is really the correct diagnosis in some cases of atypical pneumonia, but unquestionably this virus is not the etiologic agent in most cases of the latter disease.

THERAPY

The symptomatic treatment is that of atypical pneumonia (see Index). Hinshaw (1940) felt that sulfapyridine was of value in a case treated at the Mayo Clinic and suggested further trial of the sulfonamides; but Favour (1943) found neither sulfathiazole nor sulfadiazine effective in his cases, and the patient of Appelbaum and Ackermann (1942) died while under treatment with sulfapyridine. Koch (1940), in Germany, was quite enthusiastic about his results with trypaflavine (acriflavine) in 7 cases, using 10 cc. of a 2 per cent solution intravenously daily for three or four days. Heilman *et al.* (1944) reported excellent results with penicillin in experimental infections, but I have not seen any report as yet of the use of this agent in the disease in man.

RABIES

(*Hydrophobia*)

Rabies is an acute infectious disease chiefly encountered in dogs, though many other animals are susceptible. It is caused by a filtrable virus associated with the so-called "Negri bodies" that develop in cells within the central

nervous system of infected animals. Webster and Clow first convincingly reported the cultivation of the virus in 1936, though apparently Kamazawa had succeeded at about the same time. A rabid animal, biting another animal or a human being, transmits the virus in saliva. Not all bitten individuals, whether among the lower animals or man, develop the disease, and it seems possible for apparently healthy animals to harbor the virus as carriers. Once the symptoms of the disease appear, however, a fatal termination after terrible suffering is certain in both animals and man. In the island of Trinidad, in 1931, it was proved that the vampire bat is capable of transmitting the virus between infected cattle and man, upon both of which this loathsome fellow feeds; it appears that a belt of this bat-transmitted rabies extends down through eastern South America as far as Montevideo.

There is little mention of rabies between the classical description of Aetius, a physician at the Byzantine Court in the sixth century A.D., and the keener observers of the eighteenth century, such as Boerhaave and his famous pupil, van Swieten, the creator of the Vienna clinic. Pasteur's first preventive vaccination with the attenuated virus of the disease was performed upon the Alsatian shepherd-boy, Joseph Meister, in July, 1885. The specific cell inclusions were discovered in the central nervous system by Negri in 1903–1904. Many years ago Sir Victor Horsley predicted that rabies could be stamped out by the muzzling of all dogs; this has often been put to the test in relatively small communities (occasionally throughout an entire national domain) and always with complete success, but a world-wide attack upon the disease in this way has yet to be organized. Rabies seems to be increasing in incidence among animals in the United States, especially in the South, where it is apparently epizootic among wild foxes. On some of the great cattle ranches in South America the disease is a serious menace.

Symptoms in the Dog.—The first sign in the fortunately relatively infrequent "furious" form of rabies is usually a change in disposition, the animal becoming increasingly restless and snappy. Then a great thirst develops, the attempts to swallow being embarrassed by a progressive paralysis of the pharyngeal muscles; salivation becomes marked and the mouth may "foam"; there is depravity of appetite and a tendency to emit low howls followed by a series of unnatural barks during which the jaws do not close; and the animal starts out on a long excursion without definite destination, usually traveling at a rapid pace and biting many inanimate and animate objects encountered en route. Finally there supervenes the paralytic stage and death. The disease runs its course in from two to eight days. In so-called "dumb" rabies, drowsiness and paralysis are more marked from the beginning, and death is mercifully quicker.

Rabies is particularly dangerous in cats, for these animals, when infected, often slink into a dark retreat from which they fly out at the passerby, inflicting severe face wounds.

Symptoms in Man.—I quote Williams' description: "Furious rabies is the most frequent form in man. For about forty-eight hours there are usually indefinite nervous symptoms, such as a sensation of constriction in the throat, or difficulty in walking or breathing, or precordial anxiety, or neuralgic pains. The temperature is slightly increased, 100.4° to 102.2° F. (38° to 39° C.). The fear of water usually develops, due to painful spasm from attempts to swallow. Characteristic reflexes may be caused by a draft of air (aerophobia) or loud noises (hyperacusis). Remissions usually occur except in the very severely

infected cases. After about forty-eight hours the excitement increases, accompanied by hallucinations and even mania, though usually no attempt is made to injure others. The mind is clear between attacks. The voice becomes hoarse, but there is no real barking. The eyes may show photophobia, nystagmus, strabismus, and unequally dilated pupils. Vomiting usually occurs. The patient may die suddenly during this stage after one to four days, but he usually passes into the paralytic stage, with muscles relaxed, jaw dropped, ropy saliva flowing, and finally into a comatose condition. Death occurs in about two to eighteen hours. Just before death the temperature may reach 107.6° to 111.2° F. (42° to 44° C.).

"Dumb rabies is less frequent in man than in lower animals. Its recognition is particularly necessary, so that it may be differentiated from the paralysis which very rarely occurs during or just after the Pasteur treatment. The onset may be convulsive, but the lower extremities feel very heavy and numb; then there quickly develops a condition of ataxia and progressive paralysis. Death occurs in from two to eight days from heart paralysis."

THERAPY

Treatment of the Dog.—A dog manifesting undoubted symptoms of rabies should be killed at once and his head shipped, either packed in ice or in equal parts of glycerin and water, to the nearest laboratory equipped to make a confirmatory search for the Negri bodies either directly or after injection into mice by the technic of Webster and Dawson. All animals definitely known to have been bitten by him should be destroyed if possible, otherwise quarantined in isolation for three months (there has been reported, J.A.M.A., 115, 1109, 1940, a presumable incubation period of 113 days in a dog bitten by a rabid dog). If, however, the dog is only suspected of having the disease he should not be killed but quarantined for observation, for a negative laboratory examination at this time would only leave the diagnosis in doubt. There need be no fear that he will recover from a "light" case during the period of quarantine, for all animals having rabies *die*. An animal showing no symptoms after three weeks in quarantine is considered not to have the disease; indeed, it is the policy of some public health departments to quarantine suspected animals only for seven to ten days since the saliva of a rabid animal does not become infectious until two to eight days before clinical symptoms appear.

Local Treatment of the Bitten Human.—Until relatively recently there has been little doubt of the paramount importance of thorough cauterization of the wound with fuming nitric acid as soon as possible after the bite has been received. But then there appeared an answer to a query in the Journal of the American Medical Association (112, 1283, April 1, 1939) to the effect that cleansing with soap and water and subsequent irrigation with saline solution might be the preferable treatment. Since the point is one of quite immense importance a controversial exchange of opinion subsequently appeared in the Journal, in which it seemed to me the proponents of cauterization came out the winners. I liked particularly the points made by Kellogg (1940), of the California Department of Public Health, which may be tersely stated as follows: (*a*) The portal of entry of rabies virus is not the lymphatics or blood stream, therefore the citing of evidence that particulate matter is carried away rapidly through the lymphatics from the site of its introduction has no validity here; (*b*) rabies virus travels centrally by way of the nerve trunks only, and very slowly; (*c*) fuming nitric acid not only destroys tissues and virus on the

surface but it also effects some penetration and destruction at an appreciable depth; (*d*) since vaccination treatment can protect against only a limited amount of virus it is important that as much be destroyed at the site of entry as possible; (*e*) considerations of scarring should have no weight, for it is just on the face, from which the virus can most rapidly reach the central nervous system, that the use of nitric acid cauterization is most imperatively necessary. However, one should not overlook the experimental study of Shaughnessy and Zichis (1943), who found that in the treatment of guinea-pig wounds that had been inoculated with fixed rabies virus, irrigation with 20 per cent solution of soft soap was just as effective as chemical cauterization with fuming nitric acid, possibly indeed slightly more effective.

Vaccine Treatment of the Bitten Human.—The incubation period of the disease in man is between twelve and one hundred days, with an average of forty. Hajare (1933), to be sure, recorded a case developing after fourteen months, and Iyengar (1935) after nearly three and one-third years, the possibility of fresh infection during the interval having been excluded in the opinion of both authors; but since such a student of the disease as Webster (1937), of the Rockefeller Institute, has said that one may unquestionably contract rabies merely by intimate contact with a rabid dog without actually being bitten, and since in the first stage of "furious" rabies a dog may become excessively affectionate instead of vicious, there would seem some reason to doubt the validity of these cases (incidentally, Schlotthauer, 1938, said, upon what authority I do not know, that whereas fluid saliva may remain infective for more than twenty-four hours, dried saliva is noninfective after fourteen hours). It is during this incubation period that the proper use of prophylactic vaccine will prevent the disease in the vast majority of cases; indeed, the failures constitute only 0.26 per cent in arm-bitten cases and 1.59 per cent in head-bitten cases, according to the latest League of Nations Health Section report (McKendrick, 1940). I am aware that there is currently some skepticism regarding the true significance of these figures since the variable factors are necessarily very many. Was the dog rabid, did he really bite the individual, did he bite through clothing, was a potent vaccine used, was the individual one of the 75 per cent who would not have developed the disease even without vaccine?, and so forth. But until there are forthcoming more significant data to be used against the vaccine than those of Denison and Dowling (1939), whose studies in Alabama brought the question to the forefront in the United States, I feel it the bounden duty of the physician to vaccinate his patient in all instances in which it has traditionally been believed such practice is indicated. One may safely wait for the appearance or nonappearance of symptoms in a quarantined dog before starting the treatment unless the bite has been received on the face or hands, in which case, owing to the short incubation period following wounds at either of these sites, the physician is usually well advised to begin treatment at once—unless, of course, he is firmly convinced of the dog's innocence. Pregnant and nursing women may be treated with safety.

It is no longer necessary to send a patient at great expense to a "Pasteur institute" for treatment, as any physician can administer the vaccine in the improved form in which it now appears on the market. The question of "live" or attenuated vaccine, as employed in the Pasteur method and several of its subsequent modifications, versus "dead" vaccine, as employed in the Semple phenol-killed method, was to be settled at an International Rabies Conference to have been held just at the time of the outbreak of War II. However, I think

the question is being settled without the Conference, for the weight of evidence is in favor of Semple (phenol-killed), or a modified Semple (chloroform-killed), vaccine upon two counts: (*a*) It is just as effective as Pasteur (attenuated) vaccines, and (*b*) it is much less likely to cause postvaccinal symptoms. There are numerous evidences, however, that commercial vaccines vary greatly in potency, and it is therefore fortunate that Webster (1941) devised a mouse-immunization test by which standardization can now be accomplished. Most of the pharmaceutical houses send out the vaccine in syringes containing 0.5 to 2 cc. ready for injection when the accompanying sterile needle is attached. The contents of a syringe is usually administered daily over a period of seven to twenty-eight days according to the severity of the case (*i.e.*, the location and extent of the wound), but it is sometimes advisable to give two injections daily for the first five to seven days—for example, in bites about the face, in severe bites on the upper limbs, in instances in which there has been considerable delay between the bite and institution of treatment, and in children in whom the virus has not far to travel from any point at which it is introduced.

The duration of immunity in man after vaccine treatment is probably no more than fourteen months, though to be sure there are very few available data on the subject. A person bitten a year or more after taking the Pasteur treatment should again go through a full course of injections. Remlinger and Bailly (1931) reported an instance of 4 full antirabies treatments in four years; a second case of 3 treatments in four years; and a third of 2 treatments in seventeen years. There were no anaphylactic accidents in any of the cases. Kohn-Richards (1939) kindly informed me that three individuals in his laboratory, having completed the Semple vaccine injections in August, found it necessary to repeat the course in the succeeding February because of a new exposure. Skin tests with the vaccine diluted 1:200 were first performed, but being negative the first injections were given. One of the individuals experienced syncope, headache and vomiting within a minute, but this was held to be a psychic reaction. In all the succeeding injections in the group, 0.1 cc. was first given as a trial dose and the injection was completed after two minutes; there were no untoward reactions.

I do not believe that the vaccine *per se* is actually responsible for many of the varied symptoms manifested by patients while taking the Pasteur treatment. In my own case, despite the fact that treatment was begun early and that the vaccine was for the most part self-administered, I was the victim of a certain unwonted apprehension, and was thoroughly weary of the irksome routine long before the course was completed. In the layman these things might easily make for a quite variegated display of neuroses. I found the intramuscular injections into the buttocks distinctly less painful than those placed subcutaneously in the abdomen.

Postvaccinal Accidents.—Two serious occurrences, however, do sometimes accompany or follow the treatment; they are paralysis and polyneuritis. Recovery is the rule, though a few persons have died in the paralysis. The percentage incidence of these severe symptoms is exceedingly low but it varies so widely in the numerous published reports that it is difficult to state a normal or average expectancy. However, it is never high enough to be considered a contraindication to the treatment and is certainly much less with "killed" than with "live" virus. Horack (1939) presented the interesting hypothesis that these rare reactions are of an allergic nature.

Treatment of Rabies in the Human.—This can only be directed toward relief of the suffering, as no cure of a proved case has ever been accomplished so far as I know. Five per cent cocaine solution may give relief if sprayed well down into the pharynx. Indicative of the degree of excitement is the experience of Hart and Evans (1939), whose patient was unable to sleep or rest and had to be shackled to the bed despite the administration of the following medication within a twenty-four-hour period: 12 grains (0.75 Gm.) pentobarbital sodium, rectally; 10 grains (0.6 Gm.) phenobarbital sodium, intramuscularly; 60 grains (4 Gm.) chloral hydrate, rectally; 1 grain (0.06 Gm.) morphine sulfate, intramuscularly. One of the sulfonamides was tried in this case without effect.

Protective Vaccination of Dogs.—In a sufficiently large-scale experiment so that the findings could be accepted as having significance, Johnson and Leach (1942) found that a single subcutaneous injection of 5 cc. of chloroform-treated vaccine had very considerable value in the prevention of rabies in dogs. There are no reliable figures available on the duration of this protection; in Johnson and Leach's study the infecting virus was introduced thirty-one days after vaccination. Molina (1938) stated that in a region in Brazil infested with vampire bats the cattle are given one injection annually for three years and appear to acquire a solid immunity.

RAT-BITE FEVER

(*Sodoku and Haverhill Fever*)

Sodoku is an infectious disease which follows usually the bite of a wild rat; other animals which have been known to act occasionally as vectors are the cat, pig, dog, monkey, squirrel, ferret, weasel and field mouse. It has long been known, and principally studied, in Japan, but authentic cases are being increasingly reported from various other parts of the world. Futaki and Ishiwara discovered the causative spirochete, *Spirillum minus*, in 1915. After an incubation period of one to four weeks, the wound site becomes secondarily inflamed and soon ulcerates, there is accompanying regional adenitis, and the patient experiences a paroxysm characterized by gastro-intestinal symptoms, fever and an exanthematous rash. The symptoms last about two days and disappear by crisis, reappearing in a few days, however, and continuing a relapsing course for several months. Sodoku is characterized by progressive anemia. The appearance of the organism in the blood of an albino mouse inoculated intraperitoneally with venous blood of the patient affords laboratory confirmation of the clinical diagnosis, but unfortunately *S. minus* or a morphologically similar organism sometimes occurs naturally in laboratory mice. The Kahn test is apparently usually positive but the Wassermann reaction shows considerable variation. Mortality is about 10 per cent in untreated cases. Hitzig and Liebesman (1944) reported an amazing case of subacute endocarditis which seemed to be certainly due to *S. minus* though the clinical course and the changes observed at autopsy were similar to those observed in cases of subacute bacterial endocarditis due to *Streptococcus viridans*.

In Haverhill, Massachusetts, in 1926, there was a small localized epidemic of cases which very closely resembled sodoku save for the fact that none of the

patients had been bitten by any animal prior to the onset of the illness. A few cases had previously been reported abroad and since the Haverhill report a few scattered cases have been reported both from this and other countries. It now appears that this entity is caused by *Streptobacillus moniliformis* (*Haverhillia multiformis*), an organism altogether unlike the spirillum which causes sodoku. Strangeways (1933) showed that both laboratory and wild rats can act as carriers of *S. multiformis;* in 1940 Albritten *et al.* reported the first case contracted through the bite of an albino rat in the laboratory. However, it is thought that in the Haverhill outbreak the organism probably entered the blood stream through the gastro-intestinal tract. In a very exhaustive study of the entire subject of the rat-bite fevers, Brown and Nunemaker (1942) stated the feeling that probably following the bite of a rat the infection is more often due to *S. moniliformis* than to *S. minus*. Rosen and Denzer (1944) offered the following differential characteristics of *S. minus* and *S. moniliformis* infection:

Spirillum minus	*Streptobacillus moniliformis*
History of rat-bite (or other animal bite)	May or may not have history of rat-bite
Long incubation period, from one to four weeks	*Short* incubation period significant; it may be long
Recurrence of local lesion with each onset of fever	Local lesion at onset of disease
Marked local lymphangitis and lymphadenitis	Mild adenopathy or none
Bluish red maculopapular rash occurs in some cases	Erythematous maculopapular rash occurs in most cases
Myalgia; no arthritis	Arthritis usually present
Serologic tests for syphilis frequently positive, particularly flocculation test (Kahn)	Serologic tests for syphilis rarely positive
Good response to arsenicals	No established specific treatment
Animal inoculation: Spirilla in blood stream	Animal inoculation: frequently arthritis and death; *S. moniliformis* in heart's blood and local lesions
Agglutination tests not of definite value	Agglutination tests usually positive
Blood culture negative	Blood culture positive

In the fatal case of rat-bite fever due to *S. moniliformis* reported by Blake *et al.* (1944) the principal visceral lesion at autopsy was focal myocarditis.

THERAPY

Neoarsphenamine or mapharsen are curative in 5 to 6 injections at intervals of one week in cases due to *S. minus*; acetarsone (stovarsol) has been satisfactorily used by mouth and also bismuth by injection, the doses of all these drugs being those employed in syphilis. In infections due to *S. moniliformis* the arsenicals have not been of value nor have any of the sulfonamide compounds. Brown and Nunemaker (1942) employed the gold salts as in arthritis in the treatment of two of their cases but it is not clear from the records that this therapy was of any value. Heilman and Herrell (1944) found penicillin very effective in the treatment of rat-bite infections of both types in mice; in the three *S. moniliformis* cases in man in which Altemeier *et al.* (1945) employed penicillin, the therapeutic response was prompt and permanent in the first two and the relapse which occurred in the other case was felt to be entirely attributable to the employment of inadequate dosage of the drug.

RELAPSING FEVER

(*Spirillum Fever, African Tick Fever*)

Relapsing fever is a remarkable disease that is caused by several varieties of a spirochete which is transferred to man by insects. The "European" variety of the disease is not conveyed by the bite of the insect but by crushing into the bite wound or the excoriation made by scratching, or by conveying the infective material to the conjunctivae; Chung and Wei (1938) showed that the excreta of these insects are not infective. In this variety it is the body and head louse, and perhaps also exceptionally flies, mosquitoes and bedbugs, which are the vectors. The disease is endemic in Great Britain, especially Ireland, the Continent including European Russia, the Balkan States and the whole of the Mediterranean basin. It has also frequently appeared in epidemic form in the Near and Far East and in Central and South America. Europe suffered considerably from it during and subsequent to War I and the experience will doubtless be the same following War II. The "African" variety, which is conveyed in biting by ticks of the genus *Ornithodoros*, and also transmitted by them through the eggs to the next generation, prevails in many "native" parts of Africa; it also occurs in Palestine, Persia, Central and South America, Mexico and in the western and southwestern states in our own country. Francis (1939) said that California reported 100 cases in a recent five-year period and that observers in Texas collected 258 cases there during the same period. Morrison and Parsons (1941) said they see about half a dozen patients with relapsing fever in Reno, Nevada, each summer and feel that probably other physicians elsewhere in the West have similar experiences. These authors reported the interesting case of a parturient woman with the disease whose baby developed it six days after its birth. Occasionally sporadic cases are seen in other states and a few have been recorded in Canada. The causative organism of the European variety, *Borrelia recurrentis*, was discovered by Obermeier in 1873; that of the African variety, *B. duttonii*, independently in 1904 by Ross, Nabarro and Milne in Uganda, and Dutton and Todd in the Congo. The causative organism in the American cases, *B. novyi*, is similar to *B. recurrentis* morphologically but dissimilar serologically. Dutton succumbed to the disease in proving its transmission by a tick. It is almost certainly established that small rodents act as the reservoir for these organisms and that certain spirochetal infections in opossums, porcupines, armadillos, monkeys, jackals, calves and horses are identical with relapsing fever in man.

The symptomatology varies somewhat with localities but there is usually a very sudden onset (after an incubation period between two and ten days), with chilliness, severe headache and pains all over the body, dizziness, gastrointestinal symptoms and a high fever. The spleen is almost invariably enlarged, the liver much less often; jaundice is not infrequent, especially at the crisis. In a variable proportion of cases there is an erythematous or petechial rash which usually starts on the neck. The symptoms last for from four to ten days, with an average of seven days, and then disappear by crisis with a drenching sweat, following which the patient seems to be in quite normal health for about a week; then comes a relapse which is usually somewhat milder than the first attack. In Chung and Chang's (1939) very useful statistical study of 337 cases in North China, there was an average of 3 to 5 relapses in untreated cases, a higher number than is usually expected, I believe, though in

rare instances twice this many have been reported. This disease offers many pitfalls in differential diagnosis, particularly in the tropics where many other possibilities confuse the picture. According to Scott (1944), the central nervous system was invaded in a relatively high proportion of cases contracted in the Libyan Desert during War II. It is easier to detect the organism in the blood of an inoculated small laboratory animal than in that of the patient; possibly Stein's (1944) new antigen may prove useful in the development of a serological diagnostic test. The death rate has been quite high in some outbreaks, but Manson-Bahr (1940) said it is usually below 6 per cent; it was 3.5 per cent in the 340 cases studied by Robinson (1944) in Abyssinia. Many complications may occur during convalescence.

THERAPY

Most men report enthusiastically upon the use of neoarsphenamine in relapsing fever. Manson-Bahr (1940) said that more than one injection has rarely been necessary in his experience, and of Chung and Chang's (1939) 281 treated cases only 16 required a second treatment; but Robinson (1944), on the basis of a large experience (see above), felt that two or three injections might be necessary, the first injection being repeated if the temperature did not fall the day after the injection or if there is a fresh rise. I see no reason why mapharsen could not be used with its usual advantages over neoarsphenamine but have seen no report of such use. Morrison and Parsons (1941) gave 0.075 Gm. of sulfarsphenamine, and after thirty-six hours an additional 0.1 Gm., to their six-day-old infant. However, some patients do not respond well or even at all to the arsphenamines. Francis (1939) reported three failures in his recent experience and reminded us that others have had similar experiences. Manson-Bahr seemed to feel that failure is especially likely to occur in the tick-borne cases, which is the type we have in the United States. Atkey (1932) gave mercury intramuscularly, and Todd (1930) bismuth, both with apparently satisfactory results. Robinson's experience indicated that vitamin K deficiency may occur in relapsing fever and that menadione should be given (see Index for methods) in all cases to prevent hemorrhage. Heilman and Herrell (1943) found penicillin highly effective in experimental infections but I have seen no report of its employment in human cases. In one of Francis' cases he employed convalescent serum (collected seven and one-half months after the donor had been infected with the Texas strain) in the ninth relapse, after which the patient recovered.

RHEUMATIC AFFECTIONS

Rheumatic Fever

(Note: The reader will probably find it of advantage to study the articles on Acute Myocarditis and Congestive Heart Failure in connection with this present article.)

Rheumatic fever is an acute disease characterized pathologically by the appearance of minute, focal, proliferative lesions in certain tissues of the body, and clinically by fever, pronounced toxemia, proliferative and exudative arthritis, usually proliferative valvulitis (endocarditis), and sometimes pericarditis, pleuritis, and a type of intercurrent pneumonia in which there are transient consolidations and the onset is without chill and often without cough (Neu-

buerger *et al.*, 1944, suggested the term "Masson body" for the rheumatic pulmonary granuloma considered to be an equivalent of the Aschoff body in the heart). The disease occurs most frequently in children of school age and is disposed to return many times, but a first attack may appear at any time from infancy to old age; in Cohn and Lingg's (1943) exhaustive study of more than 3000 cases it was found to begin more often at about eight years than at any other age, and that at fifteen, which was the mean age at onset, 70 per cent of persons afflicted had already acquired the disease. These workers found that in youth the onset of the disease is characterized by polyarthritis in about half and by carditis or chorea in about one third of the cases, whereas in adult life the onset is characterized chiefly by polyarthritis and, with advancing age, by the appearance of valvular lesions alone. Rheumatic fever is encountered with greatest frequency during the late winter and the spring months in the United States, in fall and early winter in England, with various seasonal distributions on the Continent. It is relatively infrequently seen indigenously in the southern United States and until recently has been considered to be almost unknown in the tropics and subtropics; numerous recent observations have dispelled the latter idea though at the same time showing that its presence in the warm lands is of a rather "spotty" nature. There is a considerable body of evidence that the tendency to contract rheumatic fever is inherited (at least one authentic case of intra-uterine rheumatic heart disease has been recorded), but the evidence that it may be a "house disease" is not very convincing. Rheumatic fever is many times more prevalent among the poorer classes than in persons better housed and fed. Martin (1940) set the incidence in the United States "conservatively" at 800,000 to 1,000,000 individuals and the annual deaths at about 40,000. The importance of dampness and low altitude as predisposing factors is undecided, but in Hedley's (1941) exhaustive statistical analysis of a large number of cases in Philadelphia hospitals no such association could be established. Rheumatic fever is extraordinarily rare in diabetics but shows no marked racial predilections. The following hypotheses regarding etiology are the chief ones currently offered: (*a*) It is caused by direct infection with one or other of the several strains of hemolytic streptococcus which have been proposed. (*b*) It is a streptococcic toxemia not necessarily accompanied by bacteremia. (*c*) It is the hypersensitive (allergic) tissue response to bacteria. (*d*) It occurs when the lowered resistance produced by streptococcic infection permits a specific virus to enter or become active in the body. Certainly it is worthy of note that in the epidemics occurring among soldiers and sailors in training camps in England and the United States during War II there was usually an apparent association with streptococcic infection; such an association has also been observed in outbreaks in schools and institutions in civilian life.

Following tonsillitis or an upper respiratory tract infection, or symptoms resembling those of acute appendicitis, or without any prodromata at all, the bout of rheumatic fever often becomes suddenly established with high fever, sweating, prostration, very painful and tender polyarthritis, and sometimes the appearance of rheumatic nodules and erythematous or purpuric skin manifestations. However, it may also begin very insidiously and the diagnosis will cause considerable difficulty. Furthermore, rheumatic heart disease occurs without having been preceded by clinically recognizable rheumatic fever; Cohn and Lingg (1943) found that before the age of ten valvular lesions alone are the first manifestation in only about 15 per cent of cases, after the age of forty

in almost 80 per cent. It is now considered that suspect should be the child who loses appetite and weight unaccountably, becomes pale and complains of muscle pain—but "growing pains," which occur principally in the lower extremities and at night, should not be confused with the joint pains of subclinical rheumatic fever. In the frank form, the successive involvement of two or three sets of joints may be completely recovered from in ten days to two weeks, but more often several sets of joints are simultaneously involved and the attack lasts much longer. Experience shows that recognizable heart involvement occurs in about 70 per cent of cases and many investigators believe that there is some degree of damage in the remaining cases even though it may not be demonstrable at the time. The experience of Boone and Levine (1938), probably according with that of many others, was that the incidence of cardiac damage of recognizable degree is much greater if there is also a history of chorea. The signs of cardiac involvement—development of murmurs, pericardial rub, elevated pulse rate during sleep, conduction changes observable in the electrocardiogram, beginning congestive failure—should be diligently sought, not because there is much that can be done to forestall or limit the involvement during the acute attack, but for the important reason that accurate knowledge of the time of its appearance and the extent of its existence will dictate the management of the convalescence. The exact place of such laboratory diagnostic aids as the sedimentation index, the Weltman reaction, formol-gel and fibrinolysin tests has not been determined, I believe. Taussig and Hecht (1938) recorded their observation of the beginning of hypertension a number of times during acute rheumatic episodes. The intensive study of Bruetsch (1944) emphasized the occurrence of late cerebral sequelae of rheumatic fever.

Hedley's (1941) statistical study of 862 cases indicated that the first attack is fatal in 3.5 to 4.5 per cent of instances, the mortality being even higher if cases of rheumatic carditis without arthritic manifestations are included. Cohn and Lingg (1943) found that when the disease begins in childhood, 69 per cent survive childhood, 35 per cent survive adolescence, 18 per cent reach the age of thirty, and 5 per cent go on beyond the age of forty-five. When the disease begins in adolescence, 85 per cent survive this age period, 55 per cent reach the age of thirty, and 21 per cent the age of forty-six or more. When the onset is in the twenties, 23 per cent, and when it is after thirty, 44 per cent, survive the age of forty-five.

De Baillou (1538–1616), whom Crookshank declared to be "the first epidemiologist of modern times," introduced the term "rheumatism." It was as recently as 1836 that Jean-Baptiste Bouillaud established what he called the "law of coincidence" between the occurrence of heart disease and this malady.

THERAPY

Nursing Care.—The patient's comfort can be much increased by transferring him to a blanketed bed and wrapping the affected joints in many layers of cotton. He should be carefully protected from the chilling to which he is liable by reason of the sweating, *i.e.*, if he is not under a cradle and cannot bear the weight of sufficient covering to protect the body from excessive evaporation from its surface, then ventilation in the room must be restricted accordingly. In so far as is possible the gown and bedclothes should be changed as soon as they become wet, but judgment must be exercised here for at times such manipulations will be little short of cruel.

The patient should be kept in bed for a month after disappearance of symptoms in even the lightest cases. Struther's (1940) recommendation seems a very sound one: keep the patient in bed until the sleeping pulse rate and the sedimentation rate have been normal, and increase in weight has been progressive, for a minimum of one month. If serious cardiac involvement has been a feature of the attack this period of enforced rest must be prolonged for as many months as is necessary to bring about as much recovery as the heart is able to manifest. "Bed rest" in these cases should be literally what the words indicate, for if the patient is allowed to go to the bathroom he is performing precisely that sort of up-and-down exercise most inimical to his chances of regaining much heart soundness (see Acute Myocarditis for an exact regimen).

Sanatorium and After-care.—The data accumulated in the survey of Wedum and Wedum (1944) tended to corroborate the growing conviction that the long bed rest and convalescent care of the sort given the tuberculous, and now considered to be of proved value for rheumatic children, should be extended to young rheumatic adults also. Beds and other facilities for all of this are certainly lacking in our country, as revealed in Hedley's (1941) study of the subject; the British are much ahead of us here. Would it not be a very satisfying thing just to set about reducing as much as possible the unhygienic living conditions and accompanying states of malnutrition from which rheumatic fever springs? Perhaps it would be less costly in the end?

Dietetics.—In the acute attack the patient may be fated for a long siege of pain which is exhausting to both mind and body; therefore his nutrition should be maintained at as high a point as possible. In the beginning the diet as suggested for use in pneumonia will suffice but as soon as the patient is willing to eat he should be given whatever of nutritious foods he will take without any planned avoidances or stresses upon either proteins, carbohydrates, or fats. The fluid allowance advocated for pneumonia patients may even have to be increased here; the salt addition is not bad either for the sweating patient is losing salts as well as water.

The Salicylates in Treatment.—That the salicylates in full doses usually afford great relief in rheumatic fever is too well known to require definite statistical affirmation. The fever promptly subsides and there is often a considerable and sometimes a complete reduction of the pain, heat, redness and swelling in the joints. We do not know how this is accomplished. Morphine will effect an equal reduction in pain but will not reduce the inflammation with so great regularity; likewise the other antipyretics, such as quinine, will reduce the fever but are not fully as effective as the salicylates in ameliorating the other symptoms. This much we do know: (1) Unlike the specific drugs and biologicals that are used in other diseases, the salicylates do not shorten the duration of an attack of rheumatic fever, nor do they lessen the incidence of valvulitis, etc. However, Boas and Ellenberg (1940) reported the successful response of rheumatic pericarditis with effusion to salicylate treatment, and Swift (1942), Conner (1942) and McEwen (1943) stated that this had been their experience also. Swift also pointed out the considerable reduction in functional valvular trauma which is obliged to result from the reduction in pulse rate accomplished by salicylate therapy. (2) Careful research has failed to show the salicylates responsible for antibody increase; indeed, the studies of Coburn and Kapp (1943) presented the possibility that the alleviating influence of the salicylates in rheumatic fever is due to their interference in

some way with the antibody-antigen reaction which they believe to underlie the tissue inflammation. (3) Salicylic acid is bactericidal in the test tube, but it is extremely improbable that it can accumulate in the tissues in sufficient quantity, under the conditions existing in the living body, to be bactericidal there during life. (4) The salicylates seem specifically to stimulate the excretion of uric acid while not affecting quantitatively to any marked degree the other common constituents of urine. This stimulation, though independent of the volume of the urine, does not begin until the drug reaches a certain concentration in the organism and ceases promptly when concentration falls below this level. The significance of these observations (Quick, 1933) in relation to rheumatic fever is unknown, but it is noteworthy that the effect on uric acid excretion begins at a lower concentration of the drug than is necessary to bring about relief in rheumatic fever.

The synthetics are fully as good as the "natural" products, as was amply shown by the independent laboratory and clinical studies of Waddell and Hewlett. Not a whit more toxic either—and the "naturals" are more expensive.

Sodium Salicylate.—This is perhaps the most used preparation. The ideal system of oral administration is to give the drug every hour for 8 or 10 doses, then stop for twelve or twenty-four hours, depending upon the gravity of the case; upon resuming, the same dose should be given every four hours until a week or ten days after the disappearance of all symptoms, when it may be discontinued by a gradual diminution of the dose. In perhaps the majority of cases the patient will not tolerate as much as 8 hourly doses, in which event the drug should be given at this time interval only until the first signs of saturation appear (tinnitus, deafness, slight visual disturbances, nausea, vomiting and perhaps diarrhea). Dosage: attempt to give 20 grains (1.3 Gm.) to all individuals of twenty years and over; reduce 1 grain (0.06 Gm.) for each year under twenty. This is of course top dosage, but is about that which Swift (1942), of the Rockefeller Institute Hospital, and Smull *et al.* (1944), of the Presbyterian Hospital in New York City, indicated that they were using. Taussig (1935) said that at the Harriet Lane Home of the Johns Hopkins Hospital she is not often obliged to give children more than 45 grains (3 Gm.) of salicylates daily.

The gastric irritation manifested by nearly all patients can be lessened by prescribing the same amount of sodium or potassium bicarbonate with the salicylate. A few physicians use capsules or powders, but for most adults—necessarily for children—solutions are preferable. Wilkinson adopts the very practical measure of giving 2 prescriptions with different flavoring for alternate use, and then changes flavorings completely every few days. I suggest the following basic prescription:

℞	Sodium salicylate	ʒiiss	10.0
	Potassium bicarbonate	ʒiiss	10.0
	Aqueous elixir glycyrrhiza	℥ij	60.0
	Syrup glycyrrhiza to make	℥iv	120.0

Label: One or more teaspoonfuls in water as directed. (Note: each teaspoonful contains 5 grains (0.3 Gm.) each of salicylate and bicarbonate.)

Leaving all quantities unchanged, this may be entirely altered in flavor by making any one of the following substitutions for the aqueous elixir and syrup of glycyrrhiza (I am employing vehicles usually liked by children):

Cinnamon water Syrup cinnamon	Water Syrup raspberry
Spearmint water Syrup glycyrrhiza	Compound elixir vanilla Syrup tolu

Water
Syrup cacao

Any of these mixtures is likely to become discolored and develop a dark precipitate upon standing. I think it should be pointed out here that Smull *et al.* (1944) found that the simultaneous administration of sodium bicarbonate and sodium salicylate prevented the establishment of as high serum salicylate level as would have been obtained with sodium salicylate alone, a fact that, in view of Coburn's work (see below) is likely to be of considerable importance.

When gastric irritation limits the dosage to less than is necessary to obtain the therapeutic effect, the drug may be given by rectum; Conner (1942) said that, since most people tolerate adequate dosage by mouth very poorly, he had found it simpler in his hospital to make rectal administration the regular routine. Heyn reported a series of 125 cases satisfactorily treated in this way. His technic follows:

"A cleansing soap-suds enema is given [I believe 1 per cent sodium bicarbonate would be better], and as soon as effective is followed by the salicylate enema given by means of a Davidson syringe and a rectal tube inserted 6 to 8 inches. The dose varies according to the size and sex of the patient and also according to the severity of the case. The first adult dose in men is usually 8 to 10 Gm. (120 to 150 grains), in women 6 Gm. (90 grains), women being apparently more susceptible to salicylism than men. . . . The amount of salicylate to be given is incorporated in 120 to 180 cc. of plain or starch water with the addition of 1.0 to 1.5 Gm. (15 to 23 minims) of the tincture of opium. The dose of salicylate may be repeated in twelve hours, when it can usually be determined whether symptoms of salicylism will appear. Usually, however, a daily enema suffices with doses increasing perhaps from 30 to 50 per cent daily until the limit of tolerance is reached. The largest daily dose which has been given has been 24 Gm. (360 grains), and the only symptoms of salicylism which have usually appeared have been tinnitus and excessive perspiration. Once or twice there has been vomiting present, which might occur in the administration of even a simple enema. Where salicylism has been excessive, it usually appears within from three to six hours and the remaining unabsorbed portion of salicylate may be washed out of the bowel by subsequent enema. This has been resorted to very infrequently indeed, and it is rare also that the rectum is intolerant of the drug."

With regard to the intravenous administration of salicylate a considerable advance was made by Coburn (1943), who pointed out that intravenous administration of sodium salicylate is required if one is to accomplish the rapid rise in plasma concentration of salicylate which he found necessary; specifically he showed that 20 patients maintained at 359 to 400 gamma salicylate per cubic centimeter manifested a prompt and progressive subsidence of rheumatic inflammation and that 20 other patients with plasma levels below 250 gamma per cubic centimeter continued to manifest an active inflammatory process. On the basis of two years' experience with intravenous salicylate administration, during which time he protected 38 rheumatic patients so treated against the

development of valvular heart disease while 21 of 63 patients treated in the orthodox manner did develop physical signs of heart disease, he recommended the following as provisional routine therapy:

Day 1: 10 Gm. of sodium salicylate in 1000 cc. of 0.9 per cent sodium chloride to be administered by intravenous drip in four to six hours.

Day 2: If the patient has any rheumatic symptoms or if the temperature has not remained normal, 20 Gm. of sodium salicylate are to be administered in 2000 cc. of 0.9 per cent sodium chloride in eight hours.

Day 3: The above can be repeated if necessary, but with the patient symptom-free and afebrile 10 Gm. of sodium salicylate are adequate.

Days 4 to 6: Sodium salicylate infusions to be continued daily until the blood sedimentation rate has made an appreciable drop: *i.e.*, about 20 per cent.

Days 7 to 30: Oral therapy is now to replace intravenous treatment, doses of 1.6 Gm. of sodium salicylate and 0.6 Gm. of sodium bicarbonate to be administered every four hours day and night, a total of 10 Gm. of sodium salicylate to be given daily during this period.

Day 30: After two weeks or more in which the sedimentation rate remains within normal limits, the patient is to be allowed a trial week at bed rest without any salicylate.

In connection with this work of Coburn's, I think it should be pointed out that his patients were young adults in whom there is ordinarily a relatively low incidence of cardiac involvement in rheumatic fever; therefore, interesting as they are, perhaps the findings do not give an entirely clear indication of what may be accomplished in children so treated. Furthermore, Coombs *et al.* (1944), while treating patients according to the Coburn plan, observed some instances of continued alkalosis of sufficient severity to interfere with kidney function and possibly to lead to permanent renal damage; they thought that the accumulation of salicylates in the blood stimulates the respiratory center with resultant hyperventilation alkalosis and that the concomitant administration of sodium bicarbonate (omitted in Coburn's plan) protects against this alkalosis through increasing the excretion of salicylates.

Strontium Salicylate.—In a patient whose stomach is revolting against sodium salicylate, equivalent doses of strontium salicylate may sometimes be substituted with advantage, but the superiority claimed for the salt some years ago was never proved.

Acetylsalicylic Acid (Aspirin).—This drug is probably more analgesic than sodium salicylate but unless guarded fully with bicarbonate it may easily induce acidosis, and it should certainly be withheld from individuals with a history of gastritis or suggestive of gastric or duodenal ulcer; indeed, Sir Arthur Hurst (1943) said that, since the performance of the gastroscopic studies by members of his group which showed that aspirin caused inflammatory gastric changes exceedingly frequently, he would expect to find a history pointing to aspirin as the direct cause of hemorrhage in at least one half of the cases of hematemesis or melena in which chronic ulcer, carcinoma and cirrhosis of the liver could be excluded. Meyer and Howard (1943), confirming the animal experimentation of Link *et al.* (1943) in which it was found that salicylic acid acts like dicoumarol in inducing a shortage of prothrombin in the blood, showed that the oral administration of aspirin or sodium salicylate to human beings in daily doses of 20 to 80 grains (1.3 to 5.3 Gm.) consistently produced hypoprothrombinemia and hypocoagulability of the blood; they also found that the administration of vitamin K with the salicylate prevented these

developments and felt it at least theoretically possible that the not unusual hemorrhagic manifestations of acute rheumatic fever might be due in some cases at least in part to the large doses of salicylate so commonly administered. Shapiro (1944) stated that while it does not seem possible to establish in man a fixed dosage of synthetic vitamin K (menadione) which will counteract the prothrombinopenia-inducing effect of a given quantity of salicylate, nevertheless in general he felt that approximately 1 mg. of menadione would counteract the effect of 1 Gm. of aspirin. Shapiro felt also that when factors such as fever, toxemia and limited nutritional intake complicate the situation, adjuvants such as ascorbic acid (vitamin C) might be needed also. I think that I should add, regarding this matter of hypoprothrombinemia and salicylates, that Quick stated to me his feeling, in April 1945, that perhaps the relationship between prothrombin reduction and the administration of salicylates is not quite so simple as it would seem from the above-cited studies; it seems to be his feeling that there are other factors, notably idiosyncratic reactions, which may explain some of these occurrences. I have seen only one report, that of Fashena and Walker (1944), in which the prothrombin level fell sufficiently low in the patient that hemorrhagic phenomena might have been expected, but in this patient bleeding was not recorded though the prothrombin rose very rapidly when salicylate administration was stopped and vitamin K was given.

Several deaths have been recorded following the administration of aspirin to individuals who were asthmatics. A few years ago Coca *et al.* and Prickman and Buchstein stated that aspirin hypersensitivity is the most frequently encountered form of drug allergy, but I think Gardner and Blanton (1940) did well to point out that the apprehension in the profession subsequent to this statement is perhaps unwarranted since the number of individuals reacting violently to this drug must surely be very small in proportion to those who take it—they found that the amount sold in the United States in the year of which they had record was 5,143,672 pounds.

Aspirin is used in the same doses and at the same intervals as sodium salicylate. It is too insoluble and unstable to be prescribed in water. Assertions have been made, however, that it may be dispensed in water by the aid of sodium citrate and that the acetylsalicylic acid is not decomposed in such a solution. Leach has shown that this is not true; decomposition does take place, and after several days the ingredients of such a solution are just the same as if sodium acetate and sodium salicylate had been used in the first place.

It was formerly held that the use of aspirin and bicarbonates together might increase instead of decrease gastric irritation, but experience has overthrown the contention. A few people experience tachycardia and possibly slight exhilaration upon taking aspirin, but the drug is not a heart depressant under the conditions in which it is used in rheumatic fever.

Calcium Acetylsalicylic Acid.—The use of this drug to replace aspirin has been urged though it would seem that its greater instability might lead to more and not less gastric irritation than the older drug; however, Douthwaite and Lintott (1938) found it less irritating in man, and Stutzman *et al.* (1941) confirmed this finding in experimental animals.

Methyl Salicylate (Oil of Wintergreen, Oil of Gaultheria).—This drug is sometimes given in about the same doses as sodium salicylate, dropping it into capsules just before use, but as it is no more efficient than the sodium salt and much more poisonous it should be used, if at all, only to paint on the joints after mixing it with 1 or 2 parts of olive oil.

The Cinchophens.—In view of the very serious type of poisoning which these drugs occasionally induce, and since we can accomplish nothing with them that is not equally possible with the salicylates, I believe I am justified in taking the position here that their use in the treatment of rheumatic fever should be abandoned.

Aminopyrine (Pyramidon).—This drug is usually fully as effective as the salicylates in reducing symptoms but like them does not influence the incidence of complications or the tendency toward relapse. It is much used in place of the salicylates on the Continent. Several observers have pointed out the advantage lying in the absence of gastric irritation under this drug, which permits certain identification of epigastric discomfort and tenderness, nausea and loss of appetite as the visceral congestive signs of cardiac insufficiency. Swift (1942), of the Rockefeller Institute Hospital, though he said he knew he was in the minority, nevertheless recommended this as the drug to be preferred in the treatment of acute rheumatic fever, his reasons being that it acts more strikingly and rapidly, that it does not cause unpleasant gastro-intestinal disturbances, and that patients can take it and digitalis together much more easily than they can take salicylate and digitalis because each of the latter induces nausea and vomiting in higher dosage. He said that he was of course well aware of the possibility of causing agranulocytosis with aminopyrine but that one was sufficiently protected if he watched the white blood count and ceased to use the drug when this count fell to 4000 or 5000 (I wonder how many agree with that statement!). Swift stated that aminopyrine dosage for the average child is a daily total of between 25 and 30 grains (1.5 to 2 Gm.) and for an adult 30 to 45 grains (2 to 3 Gm.); he felt it especially important with this drug to administer it from early morning until late at night, *i.e.*, giving the first dose when the patient awakes in the morning and the last dose at 8 or 9 o'clock at night instead of allowing a twelve-hour interval to elapse between the night and morning doses.

Digitalis.—It is probable that today very few individuals would champion the viewpoint widely held a few years ago that digitalis was contraindicated in the presence of active carditis in acute rheumatic fever, but Wilson (1940) in her fine monograph on rheumatic fever well made the point that conclusive evidence as to the favorable or deleterious action of the drug is difficult to obtain since it is often impossible to evaluate in the individual case the role of digitalis on the one hand and the effect of cessation or progression of the rheumatic process on the other. For the details of digitalis therapy see the article on Congestive Heart Failure.

Miscellaneous Measures.—*Sulfonamides.*—We now know with certainty through many confirmations of the studies of Swift *et al.* (1938), and Massell and Jones (1938), that not only are these drugs of no therapeutic value in rheumatic fever but that in addition their use may actually aggravate the severity of an attack.

Penicillin.—The careful studies of Foster *et al.* (1944), Watson *et al.* (1944), and Twiss (1944) produced no evidence that this agent is of value in the treatment of rheumatic fever.

Nirvanol.—It seems that undoubtedly this agent has a definite antirheumatic effect in some patients, but it fails in many instances and I see no reason for ever preferring it to the salicylates.

Sulfur and Iodine.—In Germany, various proprietary combinations of these two drugs have been employed by a few clinicians, but I have not as yet found a carefully controlled study of their effectiveness.

Antistreptococcus Preparations.—Both in this country and in England small groups (Swift *et al.;* Small; Collis and Sheldon; Wasson and Brown), employing serums and vaccines variously prepared in their own laboratories, have felt that they were at times able to induce a state of resistance in their patients. Wilson's (1940) analysis of her findings with such agents did not, however, reveal them to be of any value.

Fever Therapy.—The earlier attempts to induce whatever nonspecific effect may be obtained by injections of milk or typhoid vaccines have now given way to the employment of the hypertherm cabinet. The latest significant study I have seen is that of Simmons and Dunn (1939), who had been employing the method for some years. Prompt and complete relief of joint pains and swelling were obtained in nearly all the cases in which these symptoms were prominent, and there was no evidence that the severity of cardiac involvement was increased. But the group studied comprised only 31 patients and these authors certainly expressed the consensus in saying that more time must elapse and much larger groups be observed before the position of fever therapy can be established. Time certainly has elapsed and I do not hear the welkin ringing in praise of this type of therapy nowadays.

X-ray Therapy.—Upon the basis of eleven years' experience in 48 patients, Levy and Golden (1937) felt that irradiation of the heart deserved a place in the therapy of properly selected cases of active carditis, but of course an experience much greater than this would be required to prove the point in a disease so variable as rheumatic fever; no one to my knowledge has come forward with a record of that experience as yet.

Convalescent Serum.—Friedman *et al.* (1938) saw no evidence of benefit from the use of this agent in 4 patients during an acute attack.

Treatment of the Anemia.—Because of the associated anemia it is usually profitable to attempt to build up the blood picture; for methods see the section on The Anemias.

Change of Climate.—Since we have no definite knowledge of the influences underlying the geographical distribution of rheumatic fever it would seem that one should be very hesitant about recommending a radical change of climate. In our country nevertheless it is not unusual for the parents of a rheumatic child to be advised to move the family permanently to a warm climate, but Southern California, Arizona, and Southern Florida appear to be about equally favored in such advice, though these are radically different types of climate. A report before the American Rheumatism Association (J.A.M.A., Oct. 16, 1937) a few years ago indicated that a shift to Florida at least is not a panacea. Tappan (1939), herself of Arizona, said that unless children of the underprivileged classes are kept out of the crowded conditions of cheap tourist accommodation when transported into a new climate, and unless they can have necessary hospital and convalescent care in the new location, they are better kept at home. She said further "there are no accurate means of gauging whether an active rheumatic infection clears more rapidly in Arizona." Obviously this whole subject needs to be studied a great deal still.

PROPHYLAXIS

Sulfonamides.—The question of the prophylactic employment of the sulfonamides resolves itself naturally into three portions: first, the employment of the drugs in a patient with tonsillitis in the hope of decreasing the liability to rheumatic fever; second, the employment of the drugs in small dosage in mass prophylaxis in the hope of decreasing the streptococcal infections including

rheumatic fever; and third, the use of these agents in the attempt to prevent recurrences in rheumatic patients.

Experience has amply proved that the administration of sulfonamides to a patient with pharyngitis or tonsillitis of presumed or demonstrated streptococcal origin does not prevent the development of an attack of rheumatic fever. Students of the disease believe that the explanation for this fact is that the rheumatic subject is sensitized by an acute streptococcal infection and that it cannot be expected that sulfonamides administered after the infection has been initiated will have any effect upon it "because the trigger mechanism has already been released." In other words, the concept of rheumatic inflammation which has gained many adherents in recent times is that the symptoms are the reflection of an anaphylactic type of reaction between antibody and the circulating antigen produced by the streptococci in their locus in the throat.

The mass employment of the sulfonamides to check the dissemination of the hemolytic streptococcus and to prevent the occurrence of numerous entities of proved or presumed streptococcal origin, including rheumatic fever, had ample trial in the armed forces during War II here in the United States. Coburn (1944), reporting on the continuous ingestion of 15 grains (1 Gm.) of sulfadiazine daily by 30,000 men at three Naval Stations during five months in the winter and spring of 1943–1944, stated that this prophylactic measure was almost 85 per cent effective in preventing implantation by *Streptococcus haemolyticus* and that approximately 85 per cent of the expected rheumatic fever cases appeared to have been eliminated by it. Holbrook (1944), reporting a similar experiment in the Army, stated that there was a 50 to 75 per cent reduction in the incidence of respiratory diseases and streptococcic infection and that the reduction in the occurrence of rheumatic fever cases seemed to parallel that of the respiratory and streptococcic diseases. It is certainly a fine thing for the war effort that all of this illness was saved by the daily ingestion of sulfonamides over a long period of time by great numbers of our soldiers and sailors, but I do not see how we can apply the experience thus gained to ordinary civilian affairs when peace returns, for surely we cannot seriously contemplate the possibility of all of our children and young adults being regularly dosed through each winter with the drugs of this group.

A much more rational measure than the above, from the standpoint of practice in a world at peace, is the attempt to prevent recurrences of active rheumatic fever in individuals who are in a quiet state after one or more bouts of the disease. To attempt to maintain a certain blood concentration of the sulfonamides in such persons, who are already sick individuals, seems to be entirely justifiable and rational. Indeed, since the reports of Thomas and France, and of Coburn and Moore, both of which appeared in 1939, there have been many recorded experiences with this sort of thing. Slocumb and Polley (1944), summarizing the literature up to the time of their writing, found that sulfanilamide had been given during 751 patient-seasons with an occurrence of acute rheumatic fever in only 1.6 per cent of the treated patients as against an occurrence of 10 to 45 per cent in the untreated controls in the various groups. Typical reports since that of Slocumb and Polley are those of Feldt (1944), in whose series no rheumatic recurrences appeared among the children who took sulfanilamide in 89 patient-seasons while there were three (7.2 per cent) recurrences among those in the 42 patient-seasons in the control series, and that of Dodge *et al.* (1944), among whose 88 children and adolescents in 181 patient-seasons there occurred 2 definite rheumatic relapses while taking

the drug regularly (an incidence of 1.1 per cent) while there were 19 definite and 7 possible rheumatic relapses among the 101 children in 138 patient-seasons (an incidence of at least 13 per cent if one includes only the definite attacks) in those held as untreated controls. Sulfanilamide is usually given in these studies from October until June, depending of course to some extent upon the climate, and in dosage from 1 to 3 Gm. daily divided into three doses. The toxicity of sulfanilamide as it is employed under these conditions has been exceedingly low; I do not think it predictable that sulfadiazine toxicity would be as low if it were to be substituted for the sulfanilamide. How long the average individual may be dosed in this way with impunity is of course not yet determined, but Thomas (1944) mentioned a patient who had taken prophylactic sulfanilamide successfully for nearly eight years.

Salicylates.—It does not seem to me that the attempt to prevent recurrences of rheumatic fever by the administration of salicylate has got very far. Reviewing this literature, I find that the statistical evidence in the series of Leech (1930), Perry (1933), Kaiser (1936) and Schlesinger (1938) hardly reveals differences of statistical significance in the treated and untreated groups, but there does seem evidence in these studies of an improved ability to gain weight and presumably an increase in general resistance on the part of the children who were dosed with the salicylates. Schlesinger's method was to give aspirin immediately upon the onset of sore throat and continue daily for four weeks; a thrice daily dose was: from five to eight years, 7 grains (0.5 Gm.); nine to fourteen years, 10 grains (0.6 Gm.); above fourteen years, 10 to 12 grains (0.6 to 0.75 Gm.). In a more recently reported study, Coburn and Moore (1942) gave 60 to 90 grains (4 to 6 Gm.) daily for one month to rheumatic patients developing pharyngitis and in whom Group A hemolytic streptococci were cultured from the throat. Forty-seven patients were treated and 139 were held as untreated controls; among the latter, 57 developed recurrences of rheumatic fever, giving a percentage of 41, whereas in the treated group there were only 16 recurrences, giving a percentage of 34. To be sure, it was said that only 1 of these patients fn the treated group developed rheumatic fever and the other 15 only showed a brief asymptomatic rise in the sedimentation rate, but since it was not stated how severe the recurrences were nor what the criteria of recurrence were in the control untreated group, it does not seem to me that this report supplied very clear-cut evidence in favor of salicylate prophylaxis.

Immunization.—Through the years the attempts to immunize patients by the employment of various streptococcal vaccines have come to nothing. To be sure, a recent report of Wasson and Brown (1943) was favorable, but much confirmation and extension of this work will have to be made before it will seem advisable to describe it as a practical measure here.

Dietetics.—As a result of their study of the dietaries of 100 rheumatic children, Coburn and Moore (1943) felt that they found indications of a close association between nutrition and rheumatic susceptibility, higher susceptible subjects having poor diets. It was not revealed, however, that these diets were consistently low in any single component but they were nearly always deficient in so many factors that the authors felt evaluation of the relative importance of any one factor was precluded. Upon the other hand, Peete (1944), as a result of his study of the dietetic habits of 50 rheumatic children compared with those of 25 normal children, plus evidence upon several correlative heads culled from the literature, concluded that rheumatic fever closely follows

the incidence of clinical rickets, which latter in his opinion probably alters the individual's immunity to the infective organism; he therefore logically concluded from his premises that the importance of adequate amounts of vitamins A and D, milk, protein, and the value of sun bathing cannot be overemphasized in the prevention of rheumatic fever. Possibly Peete is right but it will take a great deal of work to prove the point.

Tonsillectomy.—Very few physicians are willing to deny that serious and even fatal flare-ups in quiescent cases are sometimes suspiciously associated with tonsillectomy. I think that the following is the consensus of unprejudiced students of this matter: until someone produces incontrovertible evidence that children without tonsils are definitely protected against rheumatism, routine tonsillectomy is not justified; but when the tonsils are large, ragged and septic (but not merely enlarged), or small and accompanied by enlarged glands, the removal of tonsils and adenoids is probably well worth while. Wilson (1940), summarizing her own data and that supplied by others, said that the evidence does not lend support to the view that rheumatic fever *per se* is an indication for the removal of the tonsils. In fact, removal of tonsils does not insure against future streptococcal infection, for, as Swift (1942) emphasized, much lymphoid tissue is left in Waldeyer's ring, and it is now appreciated that streptococcal rhinitis may be as important a precursor of rheumatic fever as is streptococcal tonsillitis.

Tooth Extraction.—Sometimes the extraction of a tooth in a rheumatic individual seems to precipitate him into subacute bacterial endocarditis. Of course if the tooth must come out it must, but it is well to recognize that its removal may be a dangerous procedure. Perhaps it is well to employ the sulfonamides in a protective fashion under the above circumstances.

Rheumatoid Arthritis

(*Chronic Infectious Arthritis, Proliferative Arthritis, Atrophic Arthritis, Arthritis Deformans*)

This is the type of arthritis which is seen in individuals in the twenties, thirties and forties more often than at any other age, beginning usually with a gradual involvement of the fingers and wrists. There are local inflammatory and proliferative changes involving primarily the synovial membrane and soft parts of the joints, great pain and tenderness and limitation of motion, migration from joint to joint, and enough new growth of fibrous tissue about the joints to cause persistent periarticular swelling of a distinctive sort which gives the joint a spindle-shaped appearance. The skin over the involved areas becomes smooth and shiny, the extremities cold and clammy, and a peculiar selective muscular atrophy takes place. In many instances the attack is preceded by anorexia, easy fatigability, weight loss, vasomotor disturbances and other evidences of constitutional involvement; during the attack there is often a low-grade fever and nearly always an increased sedimentation rate, the latter usually proportional in degree to the severity of the involvement. Ankylosis, which is very common in this type of arthritis, usually does not appear until after the patient has suffered several attacks. Rheumatic nodules appear frequently, especially in the elbow region. The form of the malady earlier known as arthritis deformans or atrophic arthritis, in which there is thickening of the capsule and marked destruction of the articulating surfaces with telescoping of the joints and ulnar deviation of the hands and fingers, is now included as

merely a very severe grade of rheumatoid arthritis. In a book of this scope it must suffice to consider the following relatively rare maladies as merely unusual forms of rheumatoid arthritis: Still's disease, chronic infectious spondylitis, Marie-Strümpell syndrome, Felty's syndrome, von Bechterew's syndrome.

It would seem that this is an infectious disease, with most of the evidence tending to incriminate some form of streptococcus, but as yet no specific bacteriologic agent has been conclusively indicated in the etiologic role. Like rheumatic fever, rheumatoid arthritis is encountered only in a "spotty" distribution in the warmer climates and the incidence is higher among the poor than among the well-to-do. A further indication of the possible relationship of these two diseases is indicated in the necropsy studies of Bayles (1943), Rosenberg *et al.* (1944) and Young and Schwedel (1944), all of whom found a quite high incidence of rheumatic heart disease in patients who had been victims of rheumatoid arthritis; however, we are very far as yet from having established the fact that a relationship between these two diseases does really exist. The careful study of Cobb *et al.* (1939) caused them to feel that grief and family worry, in addition to poverty, bear more than a chance relationship to the onset and exacerbations of the disease; indeed there is an increasing group of observers who look upon the arthritic phenomena as representing a psychosomatic reaction. Evidences of an hereditary factor and of a predisposition to develop rheumatoid arthritis seem to be increasing as our knowledge grows. Differences in racial susceptibility are not pronounced though somewhat fewer Negroes are affected than whites. There is still much confusion among students of this malady. Some point to the frequency of constipation and the low gastric acidity of many of these patients and consider that these things are of at least great contributory importance; decreased functional capacity of the liver is also alleged to be a frequent occurrence. Others cite hypothetic metabolic derangements affecting carbohydrates, proteins, calcium, sulfur, etc. Vitamin deficiencies have been suggested, and the possible allergic or endocrinopathic nature of the malady has not been overlooked. To date, however, the importance of none of these things has been proved. Perhaps the belief that has had the largest number of adherents in recent times is that the disease is initiated from some primary focus of infection in the teeth, tonsils, sinuses, gallbladder, cervix, prostate, colon, or elsewhere—but this viewpoint has been so often challenged, and of late so openly deserted by many of its former adherents, that I think it nowadays no longer holds the forefront of attention. Rheumatoid arthritis does not often directly kill, but it maims and impoverishes and lays a heavy toll upon its victim's fortitude and upon the purse of his community.

Sydenham, in 1683, differentiated rheumatic fever, gout, and chronic rheumatism, but the first sharp delineation of the essential pathology of rheumatoid arthritis was that of Nichols and Richardson, in 1909.

THERAPY

Rest.—It is certainly the consensus among those who have had the largest experience that rest is the most important single item in treatment. Patients know this too, and those who must remain ambulant as long as possible always seek to avoid fatigue since they early learn that it invariably aggravates their symptoms. A complete rest cure of six months to a year is the ideal thing and one which has undoubtedly greatly benefited many patients, perhaps even permanently cured a goodly number. But unless the rest can comprise mental

as well as physical repose, both often best accomplished away from home, the compromise must be made of persuading the patient who remains active to lie down for an hour or two in the middle of the day and to retire to rest if not to sleep very early each evening.

Relief of Pain.—It is a rare case in which the salicylates are not used: if bedridden, much as in rheumatic fever; if ambulatory, of course in greatly reduced dosage. Unfortunately the relief afforded is often very slight. However, many arthritics take very large doses of aspirin over many years and claim that without it their lives would be unbearable. It is my feeling that here, as in rheumatic fever (*q.v.*), the cinchophens should not be used. Obviously morphine or dilaudid should not be used; indeed, Rynearson and Hench pointed out a number of years ago that in conditions diagnosed as rheumatic in which it is necessary to use morphine one had best reconsider the diagnosis. Sometimes, when pain is preventing sleep, 1 grain (0.06 Gm.) of codeine sulfate in combination with a hypnotic will satisfactorily control the situation. Physical therapeutic measures have a considerable though often temporary analgesic effect. Short and Bauer (1942) felt that further trial should be made of the injection of 2 per cent novocaine solution above the affected joint, for they said that at times the temporary relief which this affords is held and the vicious cycle of pain, muscle spasm and disability is apparently broken for awhile. Crowes' (1944) statement that he had accomplished the relief of pain in three-fifths of 280 painful joints into which 1 per cent acid potassium phosphate in isotonic saline solution had been injected is certainly interesting, and his work will constitute a real contribution if it can be confirmed.

"Building-up" Therapy.—Most rheumatoid arthritics are of the lean and scrawny type, many of them are grossly underweight and hypochromic anemia of some degree is practically a constant finding. Certainly it is rational practice to try to "build up" such people and would be even though they did not have arthritis. But we have as yet no magic wands that are worth the waving. All the present pother about vitamin stuffing is still just pother. The study of Bayles *et al.* (1943) of the dietary history of 31 patients with rheumatoid arthritis, for the year before the definite onset of their disease process, revealed that their food intake was essentially the same as that of a cross section of families in the North Atlantic states, and it would therefore seem that if there is any food factor deficiency contributory to the onset of rheumatoid arthritis it must consist in an increased total requirement of the patient rather than in a specific deficiency in his average diet. In treatment so far as we are as yet aware the patient needs only a good nutritious diet. Unfortunately the anemia is not usually easily corrected with either iron or liver preparations. Transfusions seem to be many times helpful in the early active cases; Thompson *et al.* (1938) also found them sometimes helpful in patients particularly resistant to treatment and whose arthritis is progressive, or in those markedly debilitated with a persistent severe secondary anemia.

Orthopedic Treatment.—It would seem the part of wisdom to have the advice of an orthopedist very early in every fulminating attack. Hench, Swaim, Holbrook, Stump and Krusen are among the leaders who have described these things in terms understandable to the nonspecialist. (*a*) The layman's and frequently the physician's belief that to "keep going" at all costs is the thing indicated to keep the joints supple is quite the reverse of what is practiced in other inflammatory conditions, in which physiologic rest is always enjoined; therefore it is wrong, and what is truly indicated is to immobilize

these joints, even with plaster casts if necessary, during the acute stage. Thus muscular spasm for the protection of a sore joint, with the resultant flexion deformity, is prevented. Complete relaxation and total body rest will take place, too, when the patient knows that his every movement will not be painful. (*b*) The use of a firm bed must be insisted upon even though this firmness can be obtained only by placing a 1-inch board directly beneath a "hard" mattress, for only thus can gross deformities be avoided in severe cases. (*c*) Fibrous adhesions apparently need not be feared if the cast is split in two days and daily passive motion is instituted and further fixation is continued or not, as the daily expert observation dictates. Even after the joints are entirely freed from splints during the day, the latter should be used to make full rest and sleep possible at night. (*d*) When to start massage and exercises, and how much exercise can be given? "During the acute phase, if an overzealous physician or even a brave patient, fearful of impending deformities, should attempt to start motion prematurely, nature's warning of severe pain and increased spasm generally prevents. The patient holds the joint as still as possible, and nature begs for help in making that rest absolute. But soon the patient will involuntarily at first, then under encouragement, warily move the joint a little. That is the signal for institution of light massage and very gentle, passive motion. As the subacute stage fades into the chronic stage, pain and tenderness further subside, and active and passive motions are increased. The rules of exercise are relatively simple: Any exercise that does not produce pain either during its administration or afterward is harmless, and can be persisted in as long as it remains painless. Any exercise that hurts the joint slightly while it is being carried out, but produces no appreciable 'hang-over,' and is not followed by a significant increase of pain, is safe. However, exercise should be avoided which, whether it produces immediate pain or not, is followed by a hang-over, such as an increase of pain that day or the next." The reason for massage is the hope of improving the circulation in the joints and neighboring parts and preserving muscle tone. Naturally, not just any "rubbing" will accomplish these things, nor is any one professional masseur as good as another; some of them are much too enthusiastic and do more harm than good in the beginning. The best procedure is to have the work started by a technician who has been properly trained by an orthopedist, and then after a while have some member of the family attempt to take over this work if she can develop the knack. (*e*) The correction of deformity in the quiescent stages of the disease by manipulation and mechanical stretching, by manipulation under general anesthesia, or by open operation, are measures in which orthopedic surgeons have made great strides in recent times, but of course the indications or procedures cannot be described here. The correction of faulty posture is also a matter calling for expert orthopedic advice.

Physical Therapy.—Because it seems to me that massage and proper exercises should be at least begun by the orthopedist, I have discussed those measures briefly above, and therefore there remain in this present category only the various methods of applying heat. The objects of heat applications are: to allay pain (how this is accomplished we do not know; ocasionally the pain is increased instead); to promote circulatory improvement through the induction of hyperemia; and to cause the patient to sweat (we do not know why this is helpful either). The ancients seem to have been busily bathing in thermal springs at the dawn of history and we do well to continue the practice. In many modern hospitals there are all sorts of gadgets for generating heat

within the body by means of anodal galvanism, faradism, diathermy and so on, but I think we can leave such appliances to the physiotherapists in these institutions, hoping that they know as much about them as they appear to do. Any physician wishing to learn the location of the nearest registered technician in physical and occupational therapy has but to make inquiry of the following agencies: American Registry of Physical Therapy Technicians, 30 N. Michigan Ave., Chicago; American Physiotherapy Association, 737 N. Michigan Ave., Chicago; American Occupational Therapy Association, 175 Fifth Ave., New York. In these pages I shall merely outline the methods for applying heat in the home without the benefit of specially trained assistants. It should be remarked, however, that Treusch and Krusen (1943), of the Mayo Clinic, found that in 92.7 per cent of cases arthritic patients carried out physical therapy in the home as prescribed and outlined for them at the Clinic, and that in 64.7 per cent of cases these treatments were continued for three months or longer; the authors felt that this indicated that physical therapy can be satisfactorily carried out at home if the measures are prescribed individually and in some detail and the patient is taught how to apply them before he leaves the hospital, but it seems to me to indicate very strongly also that they were of benefit or else the patients would not have continued to use them for so long a period.

The Complete Bath.—The patient gets into the bath with its temperature at about 100° F. (38° C.) and during fifteen minutes the temperature is raised to about 104° F. (40° C.); he stays in the bath for a total of thirty to forty-five minutes and then goes to bed and continues his sweat under plenty of cover. The bath should be begun with the stomach empty but after it is over light food may be taken; while in the tub a cold wet towel should be kept wrapped around the head to prevent headache and faintness. Such baths should not be given to patients with arteriosclerosis, any sort of cardiac abnormality, or organic nervous disease, and they should be employed with extreme caution in asthenic or debilitated individuals.

Six pounds of ordinary salt added to the bathtubful of water (50 to 60 gallons) will give a salt content equivalent to that of the sea. Such a brine bath retains heat longer and probably stimulates perspiration better than plain water; its buoyancy is of assistance also if active movements are to be performed. The mustard bath ($\frac{1}{2}$ ounce of mustard per gallon of water, mixed first with a little cold water) is somewhat too irritating for most skins.

The complete bath would seem to be the simplest way of applying fever therapy, the temperature rising considerably due to temporary abolition of surface radiation.

The Partial Bath.—All of the local effects of hot bathing can be obtained by simply immersing the affected joints, such as fingers, wrists, ankles, etc., in a suitable receptacle. For a hip bath the patient may sit in an ordinary clothes-washing tub with the feet and arms outside; if the feet are then placed in another tub or bucket of hot water and the whole ensemble except the head is covered by a blanket, he is taking the famous "sitz bath" (of course this can be accomplished by having him sit in a partially filled bathtub with knees up and only hips and lower legs and feet in the water; but the modern tub against the wall is difficult to drape). The temperature of such partial immersion baths may be safely brought up to 110° F. (43.3° C.), but it should be remembered that general sweating of the body is likely to be induced and the patient

should be protected against its excessive evaporation and the consequent chilling.

Contrast Baths.—In rare instances the patient seems to profit by the alternate application of heat and cold. This can of course be simply accomplished by placing the extremity in hot water, then cold water, then hot water, etc.; but one must always begin and end with heat.

The Paraffin "Bath."—A sufficient number of cakes of paraffin (procurable at any grocery) is melted in a receptacle of the proper size and shape to admit the hand or foot, and then, just when a thin film has begun to form on the surface of the paraffin, the member is plunged in, held in the hot paraffin for ten to thirty seconds, removed and, after the coating has dried in thirty to sixty seconds, returned to the paraffin bath. This is repeated until six or eight coats have been applied. The member is then placed at rest on a cushion and covered with a blanket. The paraffin is easily removable—it is usually retained in place for thirty to sixty minutes—because much perspiration gathers beneath it.

A modification of the above method is to paint many coatings of paraffin over the joint with an ordinary paint brush or a swab on a stick. Krusen (1940) wrote favorably, too, of applying alternate layers of gauze and paraffin which may then be left on as a comfortable support until the treatment is repeated next day. It is best either to shave or oil a hairy region before applying paraffin.

Packs.—Mustard: Make a paste by stirring a teaspoonful of mustard into tepid water; then stir this into a pint of nearly boiling water. A towel wrung out of this hot mustard water is applied to the part, covered with a blanket and left in place for five to ten minutes. Afterward sponge away all the remnants of mustard with warm water and under no circumstances apply this pack at all if the skin is broken.

Mud: Add powdered fullers' earth (kaolin) to a receptacle of nearly boiling water until this acquires poultice consistency, having previously placed close at hand a piece of linen or cotton cloth covered with a layer of gauze. Quickly transfer the mass to the cloth in a layer about 1 inch thick, mold it about the affected part, cover with a blanket, and leave in place about thirty minutes.

Radiant Heat.—In the hospitals there are electric light cabinets and infra-red lamps which are very effectively used. Ray (1936), whose excellent series of articles much assisted me in the original preparation of this outline several years ago, described a simple home substitute provided by making two bricks red hot in a fire and placing them at the bottom of an old bucket. "Over this a limb may be supported, covered by blankets; a knee, elbow, wrist, ankle, foot, or hand can thus be exposed to infra-red rays which are just as efficacious as those derived from a more expensive electrical apparatus." Krusen's (1940) inexpensive homemade baker may be constructed of a piece of ordinary sheet tin curved in a roof-like fashion on a framework of strap iron or rods. Two double electric sockets are attached to the the under surface of the roof and the necessary wiring is installed. Bulbs of 60 or 120 watts may be used to obtain the desired amount of heat.

Climatic and Spa Treatment.—There comes a time in the course of most cases of arthritis when the patient will be benefited, psychically if not otherwise, by a trip to a spa, but unfortunately the economic strain of such a sojourn cannot be borne by the majority of individuals. Likewise, those who can move permanently into a warm climate, not necessarily dry, may be bene-

fited if the malady is not too far advanced, but see *Change of Climate* in Rheumatic Fever.

Employment.—Some years ago Coulter pointed out that occupational therapy can be applied at home if the patient, physician and family will earnestly set about finding tasks which will provide opportunity for the repetition of exact motions—for example, for bending and straightening the leg at work while the patient is thinking about his job, he suggests refinishing wooden furniture, which involves constant squatting and rising as the rungs and other parts of a chair are worked upon. How to return each crippled individual to a job in which he can regain economic freedom at a cost to his self-respect that is not excessive is a problem indeed, but the physician must help bear the burden of trying to solve it.

Eradication of Foci of Infection.—This is by no means a strictly modern approach, for according to Osgood (1940) we find the physician to Ashurbanipal, King of Assyria in the seventh century before Christ, advising his master as follows: "He will speak the truth with the king as the king demanded: the pain in his head, his sides and his feet has come from his teeth; they must be extracted." Nowadays, even if a physician knows little else about the disease, he is sure to know that "eradication of focal infection" is absolutely indicated. But why—if this indication is so absolute and in consideration of the almost routine fashion in which it is met—do we not see more uniformly good results? Occasionally, to be sure, the response is startling and there is a case to report and moralize upon, but it does not happen with any great frequency; and sometimes an exacerbation is unquestionably initiated. Solis-Cohen opined a decade ago that in "eradicating" a focus we do not get rid of the bacteria anyway, for they continue to live and multiply in the tissues surrounding the area from which the "focus" was removed; perhaps he was right. Even many of the enthusiastic advocates of this type of treatment are now admitting its futility in cases that are far advanced, and some of the leading students of arthritis seem to be changing their minds. In 1933, Cecil wrote "the keystone of the modern treatment of rheumatoid arthritis is the elimination of infected foci." In 1938, he and Angevine were saying "the time has arrived for a complete revaluation of the focal infection theory." Then, in a Cornell Conference on Therapy in 1941, Cecil said: "In respect to rheumatoid arthritis the theory of focal infection is generally discredited because students of arthritis have found: first, that in a great many patients the disease develops without any association with foci and, second, that those who have had foci of infection removed have obtained only temporary benefit, if any at all. The disease goes on its progressive course, even after tonsils, teeth, and other suspected organs have been removed." Reimann and Havens (1940), in a critical appraisal of the entire subject of focal infection and systemic disease, were unable to make out a case in favor either of the theory or of the routine "eradications" based upon it. In their authoritative review, Short and Bauer (1942) very clearly expressed the viewpoint that the attempt to eradicate a focus of infection in the arthritic patient is indicated only as it would be to improve the general health of a patient without arthritis.

Miscellaneous Measures.—Some years ago Miller (1936) performed a fine service by reemphasizing that: (*a*) rheumatoid arthritis is characterized by a variable onset and a course in which remissions are not uncommon; (*b*) therefore any claims for the effectiveness of a remedial measure can be valid only if the measure was applied in a study employing the control method and then

only if the improvement consistently sets in shortly after the treatment is started. With these things in mind the following measures do not seem to warrant description as major items.

Fever Therapy.—Apparently such relief as is afforded by fever therapy occurs in a very variable proportion of cases and is only temporary in practically all instances. I know of no one in an authoritative position in this field who is now recommending fever therapy as the method of choice.

Vaccines.—A few sanguine individuals are still hopeful of establishing the value of vaccine therapy in arthritis; one can only say that they are a long time about it.

Attention to the Gastro-intestinal Functions.—There are those who urge that not only should constipation be vigorously combated but the colon should also be systematically irrigated; they are decidedly in the minority among leading students of the disease. Since the recognition of the small amount of acid in the stomachs of some arthritics, the routine administration of hydrochloric acid as in achylia gastrica has become popular in some quarters, but I have seen no reported evidence of substantial accomplishment with this measure.

Treatment of Brucellosis.—Goldfain (1938), in Oklahoma, found a high proportion of arthritics had brucellosis also and concluded that treatment of the brucellosis helpfully influences the course of the arthritis. However, Green and Freyberg (1941) were unable to show a significant coincidence of the two diseases in Michigan; indeed, not a one of the 25 patients with characteristic rheumatoid arthritis whom they studied had any evidences of brucella infection.

Sulfur Therapy.—Freyberg *et al.* (1940) and Abrams and Bauer (1940) thoroughly laid this ghost.

Gold Therapy.—It seems to me only fair that the reader be apprised of the cause of the renewed interest in gold therapy in our country. A good many years ago the French began using gold (to their own satisfaction at least) in tuberculosis and since they feel there is probably an association of some sort between tuberculosis and rheumatoid arthritis, they logically tried gold in the latter also. Forestier was the outstanding leader in this work who, after numerous publications detailing successful employment of gold, came to this country and lectured on the subject. There followed a number of trials of the agent by American clinicians, but the reactions were so frightening that gold therapy was quickly abandoned here. But the French and others on the Continent continued to report their satisfaction with the remedy and then the British took it up. But we still held off and finally the British lost patience with us and editorially as well as during personal visits to our shores let us know they thought we were not giving a good agent the fair chance it deserved. Of course had real "foreigners" pursued such tactics with us the result could only have been a strengthening of our opposition, but when friends with whom we have traditional ties in medical and many other fields so persistently nagged us it was only natural that here and there a clinic director said in effect "Oh, all right," and began a new study of the drug.

Results.—There are now available in the American and British literatures a number of quite enthusiastic reports regarding the results to be obtained with gold therapy, and if one is to believe the Continental reports cure or striking improvement can be obtained in 80 to 90 per cent of cases. But I do not like enthusiasts, having been one myself in my youth, and shall therefore

only state here that the most earnest and conservative student of this subject in the United States, namely Freyberg, formerly of the University of Michigan and now at the Hospital for Ruptured and Crippled, New York City, stated that of his patients given one course of gold therapy, 55 per cent showed moderate or marked improvement or were apparently arrested and that two courses of treatment gave slightly better results, 68 per cent showing improvement of this degree. Now these figures do not seem to me very impressive for several reasons: First, they were not obtained in a controlled series in which alternate cases were left untreated for comparison. Second, the results of nonspecific (*i.e.*, nongold) therapy are just about as good, for Short (1942) recorded that 53 per cent of a series of 300 arthritic patients treated in the Massachusetts General Hospital experienced more or less satisfactory improvement after receiving nothing but "general therapy." Third, there is still great divergence of opinion regarding dosage, a fact which in itself seems to me to constitute an indictment of gold therapy in its present status. And fourth, why is it that, if this is a specific chemotherapeutic agent whose true value will only be realized when we learn fully how to use it, which is the position taken by most of the champions of the gold salts, it is taking us so long to acquire the necessary knowledge?

Reactions.—The present attitude in the United States is that gold therapy is so dangerous that it should be undertaken only in cases refractory to the more usual types of treatment and even then only if the patient and family understand the risk that is being taken. When last heard from before the outbreak of War II, Forestier was impatient with this conservative tendency in us, but this is nothing new for we have always been more cautious in the use of potent drugs than the Continentals. The organs especially affected are those through which the gold is excreted, the kidneys, stomach and intestine. The following reactions occur: temporary increase in pain, skin eruptions, exfoliative dermatitis, edema, stomatitis, conjunctivitis, iritis, "gold bronchitis," gastro-enteritis, hepatitis with jaundice, albuminuria, acute nephritis, hematopoietic damage (agranulocytosis, leukopenia, platelet reduction, purpura, aplastic anemia), neurologic and psychic manifestations. There is no way of anticipating, preventing, or specifically treating these reactions. And some of the patients die. Short's (1942) review of the reported cases in the literature showed that 1 person in 200 (0.5 per cent) of the patients given gold dies as a result of the injection. Significant toxicity occurred in 42 per cent of the patients of Cecil *et al.* (1942), 81 per cent of those of Furlong (1942), 74 per cent of those of Short (1942), 38 per cent of those of Price and Leichtentritt (1943), and 42 per cent of those of Rawls *et al.* (1944), but Freyberg *et al.* (1942) stated that serious toxic reactions occurred in somewhat less than 10 per cent of the patients treated.

Contraindications.—The principal ones seem to be the following: pregnancy, severe anemia, history of purpura or agranulocytosis, ulcerative colitis, nephritis, diabetes, hepatic disease, congestive heart disease, chronic skin affections such as eczema (but not psoriasis), active tuberculosis, hypertension. Old age and arteriosclerosis do not seem in themselves to constitute contraindications. Parr and Shipton (1937), in Australia, considered that thin anemic patients with cold clammy skin should not be given gold therapy, but Tegner (1939), one of the advocates of the drug who visited us from England, did not agree with this. It would seem wise to withhold the drug in patients with an allergic history.

Dosage.—The conventional method of administration of the gold salts is to inject the chosen agent weekly, beginning with 10 or 15 mg. and increasing the amount gradually to 100 mg., this latter dose being continued weekly until 1 to 1.5 Gm. of the drug are given. Treatment is usually then discontinued for six to twelve weeks, following which one or more similar courses are given. Of the three salts most used in the United States, sodium-gold-thiomalate (myochrysine), sodium-gold-thiosulfate, and gold-thioglucose (solganal B.), only the thiosulfate salt may be given either intravenously or intramuscularly, the other two being given only intramuscularly. Freyberg *et al.* (1942) thought that the conventional 100 mg. weekly dose of gold-sodium-thiomalate was probably excessive in many instances and that this preparation should be used in weekly injections of not more than 50 mg. of the salt (25 mg. of gold); they felt also that the weekly dose of gold-sodium-thiosulfate should not exceed an amount which would contain 25 mg. of gold, *i.e.*, 65 mg. of the salt. Regarding thioglucose, Rawls *et al.* (1944) felt that good results could be obtained by giving only 25 mg. a week throughout the series of injections and in no case did they ever increase their dosage above 50 mg., claiming to have obtained as good results as others with larger doses.

Other Drugs.—Trommer and Cohen (1944) employed prostigmine for the relief of muscle spasm in 19 cases much as it is used in poliomyelitis (see Index); in 13 of the 19 cases sufficient muscular relaxation was said to have been obtained to permit active as well as passive motion in the affected joints with less pain, though there was no demonstrable effect on the pain produced by the joint lesion itself. Boland *et al.* (1944) gave large doses of penicillin intramuscularly every three hours day and night to 10 soldiers with early but progressive rheumatoid arthritis and obtained no evidence that the treatment was of any value whatsoever. I do not feel that any of the following at present merits the space that a full discussion of the methods of its employment would require: calcium, acetyl-beta-methylcholine (mecholyl), vitamins, alkalis, iodides, arsenic, bismuth, chaulmoogra oil, histamine, bee venom, cobra venom, calcium or ammonium ortho-iodoxybenzoate, endocrine products (except when used in cases occurring concomitantly with the menopause), sulfonamides, bile salts, activated vaporized sterol (ertron).

X-ray.—Freyberg, who gave the *coup de grace* to sulfur therapy, more recently accomplished the same thing with regard to x-ray (Smyth, Freyberg and Peck, 1941). Selecting patients in as many instances as possible who had pairs of comparably affected joints, 74 were given roentgen therapy. In some instances treatment was applied to only one of the pair of joints, in other instances to both but with one screened so that no x-rays reached the skin (a test for psychic effect of the procedure). The effects were studied from the standpoint of subjective and objective changes and also through frequent sedimentation rate determinations and diagnostic x-ray examinations of the joints. The results were so unpredictable and unreliable that they decided to abandon this type of therapy except in rare obstinate cases "or cases in which a psychic effect is desired."

Effect of Jaundice.—Occasionally an attack of rheumatoid arthritis will be suddenly terminated upon the appearance of intercurrent infection or, according to Rawls (1939), urticaria, but the most astonishing recent development in the disease has been the observation of the regularity which characterizes its disappearance when jaundice—from whatever cause—appears. Not only does the pain suddenly and completely disappear but the stiffness and swelling are

also markedly decreased. Hench, of the Mayo Clinic, has been the principal one to report this phenomenon (corroborated by many others) and I include mention of it here not because it has any present practical therapeutic significance but for the reason that, as stated by Hench, ". . . viewing nature's easy victory over a perversely stubborn disease, it suggests that the arthritis process is not as irreversible as might be supposed. It suggests that the long weary journey which many of our patients must today traverse to reach the inactive stage may not be an inevitable necessity. It raises the hope that we too may sometime find the way to score an easy victory if only we can map out nature's short cut."

Effect of Pregnancy.—The observation that arthritis may recede before pregnancy has been made a number of times, but it was only a few years ago that Hench recorded the actual occurrences in a series of patients. Twenty of the 22 patients experienced striking, generally complete relief during their 34 pregnancies, each experiencing it each time she was pregnant with one exception, that of a tubal pregnancy. The relief lasted for variable periods after delivery.

Palindromic Rheumatism

In 1940 and again in 1944, Hench and Rosenberg reported their observation of a new syndrome to which they gave the name palindromic rheumatism, which seems to mean merely recurrent rheumatism. In this malady there are brief recurring attacks of pain, swelling, tenderness and redness in or about a joint, without fever or other notable evidences of constitutional disturbance, often with marked temporary disability but invariably complete recovery and no permanent injury to the joint. The attacks start very abruptly and usually last only from a few hours to a few days, though in 2 of the 34 cases of Hench and Rosenberg the symptoms sometimes persisted for two to three weeks. In some of the patients attacks occurred almost daily, in some they came at intervals of several weeks, and in others there were long intervals of freedom up to six months. In the 34 patients the average duration of the disease had been seven years, varying from less than a year to more than twenty years. Joints seemed to be attacked very capriciously and unpredictably, but in 90 per cent of the cases only one joint was involved at a time. The involved joints are usually only moderately swollen as a result of both effusion into the joint cavity and localized periarticular swelling; fibropurulent exudate in the joint cavity and acute inflammatory reaction in the synovial membrane were revealed by biopsy during an attack in two cases. In about a third of the cases there appeared, in addition to the joint swelling, certain small well-demarcated swellings in the soft tissues not necessarily near the joint involved, these soft tissue swellings usually disappearing within twenty-four hours. The only laboratory findings during any of the attacks were relative lymphocytosis and moderate transient increase in the sedimentation rate.

In these cases of Hench and Rosenberg the attacks seemed to bear no relationship to acute infections, and removal of what foci of infection could be discovered did not affect the disease. Vaughan (1943) reported 10 cases of food allergy which seemed to fall into this palindromic rheumatic group, but Hench and Rosenberg (1944) did not feel it likely that allergy played an important etiologic role in their cases, and they quoted Prickman of their group at the Mayo Clinic as being also of this opinion.

THERAPY

Hench and Rosenberg tried a good many measures and had success with none of them.

OSTEO-ARTHRITIS

(*Hypertrophic Arthritis, Degenerative Arthritis*)

This is the type of arthritis characterized by the presence of Heberden's nodes and the gradual onset, in individuals in or past middle age, of stiffness and limitation of motion, some muscle spasm and pain which may be both localized and radiating or referred. There is degeneration and thinning of the cartilage with new growth of bone around the edges of the joints involved, principally the spine, knees, knuckles, hips and shoulders, but without fusion of the articular surfaces. In contradistinction to rheumatoid arthritis, which is a disease of the synovial membranes and probably infectious, this is a non-infectious disorder of cartilage and bone. Very likely it is merely one of the phenomena of senescence, symptoms developing only when a joint that is wearing out continues to be subjected to chronic trauma; it has been alleged that the state is seen most frequently in the laboring classes but I do not know that a careful study would prove this to be true. Apparently osteo-arthritis may occur as the result of an acute traumatization of a joint. Another form is that sometimes distinguished as "menopausal arthritis," in which women at the cessation of the menses, whether this occurs normally or after castration, have the type of muscle and joint symptoms known as arthralgia. In this menopausal type, if the woman grows suddenly excessively stout it may be that pain and stiffness is experienced only in the knees when they are obliged to support this unwonted weight, but the symptoms are oftentimes present in other joints as well.

Osteo-arthritis is the oldest disease of which we have indubitable record—in the skeletons of beasts that preceded man on the earth by several hundred millions of years, in the "ape-men," in earliest man, in man through all the ages.

THERAPY

The principles of treatment are the same as those which obtain in rheumatoid arthritis except that bony ankylosis and flexion deformity do not occur in the disease under present consideration and it is altogether a less virulent-seeming malady. Indeed most of its victims have no symptoms at all, and in many patients—this is especially true in the menopausal cases—measures directed toward reduction in weight constitute the chief therapy. Latterly, the increasing use of estrogenic substances is giving relief in some of the menopausal cases (see article on the Menopause).

GOUT

Though there are many variants, the classical development of gout is about as follows: An individual—in more than 95 per cent of instances a healthy robust man in the decade between thirty and forty—is suddenly awakened in the night by a severe pain in one of his great toes, a pain that rapidly increases until it reaches almost unbearable proportions; then at about daybreak—at "cock crow," said Sydenham (1683)—great relief is more or less suddenly experienced and the patient usually falls into a heavy sleep. On awaking later in the morning he finds that the affected metatarsophalangeal joint is some-

what swollen, is red and has a glistening appearance, and that the veins around it are peculiarly distended. Throughout the day the swelling increases and the joint becomes very tender but the pain is only slight or may be entirely absent. Then with the night comes a recurrence of the torture. Usually an attack lasts only a few days but is occasionally protracted for a period of several weeks; it is not infrequent for it to shift from one great toe to the other or to some other joint, or for both toes to be affected at the same time, or for some joint other than that of a great toe to be first affected; the most rarely affected joints are the hips, shoulders and spine. A slight rise in temperature is usually noted. Upon subsidence of the attack, the affected joint is completely restored both in appearance and function. The patient will then be symptomless for a period of months or years—the average time is about one year—whereupon the second attack is experienced. Thereafter, attacks occur with increasing frequency until a state of chronic gout is reached. This is characterized by marked swelling and deformity of the joints due to the gradual deposition of sodium monourate in the cartilages and ligaments. Strange to relate, it is usually not the toes that are thus involved but the joints of the hands and elbows most frequently; the olecranon and prepatellar bursae may also be distended with nodular masses. There is relatively little pain when this chronic stage is reached. In addition, in most instances, tophi containing urate deposits appear in the skin, most characteristically in the fleshy lobe of one or both ears; these tophi sometimes ulcerate.

Gout is apparently associated with a faulty uric acid economy, but the exact nature of this association is not understood. Uric acid is a normal constituent of the blood and the urine, but in gout the amount in the blood is almost always abnormally high and in the urine abnormally low; however, this alone is not sufficient to account for the development of the clinical picture, for the same conditions obtain in other diseases, namely chronic nephritis and leukemia, without gouty symptoms appearing. Furthermore, the substance is not itself highly toxic since it may be quite freely injected intravenously. In favor of the belief in the direct relationship of uric acid to the disease is the fact that a purine-free diet is considered beneficial in treatment, and that a diet low in protein and carbohydrate but high in fat will increase the amount of uric acid in the blood and markedly exacerbate the symptoms; Lockie and Hubbard (1935–39) proposed the use of this latter diet as a diagnostic aid in doubtful cases. Most clinicians hold that some other, as yet undiscovered, agent is at work in the causation of the disease; allergy and a disturbance in the vegetative nervous system have both been proposed. That heredity, overeating, the use of alcohol and lack of exercise are factors of importance has long been recognized. Many cases seem to be in some way associated with lead poisoning and in other instances it appears that a brief period of dietary or bacchanalian excess or of physical stress or strain, or the subjection to a major surgical operation, or the taking of an unusual drug, precipitates the initial attack. Hebrews seem particularly prone to develop the disease; Negroes are rarely affected. Patients do not die of the symptoms of the disease which we are so far able to recognize, but in the early stages they suffer greatly and are severely crippled later on. Gouty nephritis (the study of Coombs *et al.*, 1940, indicated that the changes are the result and not the cause of the metabolic dyscrasia) and renal colic from urate stones or gravel are recognized complications and there is strong suspicion of a greater frequency of vascular diseases in gouty than in nongouty individuals.

The distribution of the disease, both as to time and place, is very interesting. Gouty deposits have been found in the predynastic mummies of ancient Egypt, and in classical times it was very common in Greece and Rome, but at the present time the Mediterranean lands know it hardly at all. In the tropics of both hemispheres, as well as in China and Japan, it is extremely rare. England has suffered from it for centuries, but it now seems to be quite rapidly decreasing there; on the Continent, too, it is said to have decreased markedly since War I. It has always been looked upon as of extremely rare occurrence in the United States, but recent studies indicate that far too many of our cases are being bandied about for many years with an incorrect diagnosis of rheumatoid or osteo-arthritis, or a mixture of these two.

THERAPY

The Acute Attack

At the height of the acute attack it is usually advisable to give a full dose of morphine or dilaudid in order to bring quick relief from the severe pain. At the same time the first dose of one of the analgesic drugs should be administered; many men also give a dose of cathartic salts at this time.

Colchicine.—The old galenical preparations, the wine and the tincture of colchicum, have proved highly unsatisfactory and are no longer used, but colchicine is looked upon by most men of experience as being a practically specific agent for relieving the pain of acute gout. The experience of Lockie (1939) is typical though it is greater than most men have had: in 75 private patients with proved gout all experienced marked relief from this drug about the time the diarrhea which it unfortunately causes set in. Dosage has to be more or less determined in each case, though Lockie's good results were obtained with the routine employment of 1/60 grain (0.001 Gm.) doses. Hench (1941) used either the 1/120 grain (0.0005 Gm.) or the 1/100 grain (0.0006 Gm.) tablets, directing that two tablets be taken initially and then one every two or three hours (in severe cases even during the night) until pain is relieved or some gastro-intestinal disturbance appears. He said that having learned his "diarrhea dose" a patient may sometimes obtain a satisfactory effect in a subsequent attack by taking one or two less tablets in the course. Bauer and Klemperer (1944) state that the diarrhea is frequently severe enough to require treatment with a drachm (4 cc.) of paregoric following each loose stool until the diarrhea is checked; bismuth subcarbonate is also sometimes employed in addition to the paregoric. It seems that other than the diarrhea untoward effects are not caused by colchicine. The agent, in the form of the crude drug, has been used since time out of mind, indeed Lockie said that it is mentioned in the Ebers Papyrus of 1550 B.C., but we have not the least notion how it works; it does not affect the uric acid level of either the blood or the urine.

The Cinchophens.—These drugs (discussed in detail in Chronic Gout below) are used by a few men in the acute attack in place of colchicine and they are often markedly effective in relieving the pain. The usual dosage is 7½ grains (0.5 Gm.) three or four times daily. Ludwig *et al.* (1938), of the Massachusetts General Hospital, and more recently Bauer and Klemperer (1944) of the same group, stated that they never use these drugs because of the risk of inducing acute yellow atrophy and the fact that colchicine is equally if not more efficacious. Lockie's (1939) patients, too, found colchicine more effective than either the cinchophens or the salicylates. But Hench champions the cinchophens (see below). These drugs increase the uric acid output when first

given, but in most cases a decrease takes place after a few days, perhaps to a level lower than the previous one.

The Salicylates.—The salicylates also influence the uric acid output in a special way (see Rheumatic Fever) but it is generally recognized that they are less effective in relieving the pain of acute gout than either of the above two agents.

Nursing Measures.—Hot or cold compresses sometimes give relief but many patients are satisfied merely to keep the joint swathed in something during the attack. Bauer and Klemperer (1944) stated that as a rule diathermy is not well tolerated. Absolute bed rest must be enjoined and massage and exercises are absolutely contraindicated. Those who adhere to purine restriction feel that the diet at this stage should be strictly purine-free; in any case the patient should be kept upon, and indeed he will rarely desire more than, liquids and soft foods, but he must be encouraged to take 3000 to 4000 cc. of liquids.

Chronic Gout

Dietetics.—It has been felt by all observers since ancient times that obesity, alcohol and gout are closely associated; in our own era the fact has been ascertained that purine-containing foods increase uric acid retention, the severity of symptoms and the frequency of attacks. Therefore the prime requisites in the dietary management of gout have been held to be that obesity be combated, the use of alcohol restricted and the purine content of the diet kept as low as possible consistently with a feeling of reasonable well-being. Latterly, however, there are those who have begun to doubt the value of such a strict regimen as satisfaction of these requisites necessarily imposes. Bauer (1943) stated authoritatively that high-purine diets do not provoke the acute illness in latent gout with any regularity and that no correlation has been possible between the degree of hyperuricemia and the frequency, severity and duration of arthritis in gouty patients. In 1938, Talbott and Coombs reported upon 2 patients who were worse when on restricted dietary than when not. Specifically, patient A, while on the metabolism ward on a low-purine diet during 3 periods totaling more than seven months had 12 attacks and severe gout on twenty-seven days, while during the following eight months at home on unrestricted diet he had 7 attacks and severe gout on eighteen days. Patient B during nine months in the hospital had 21 attacks and spent thirty-nine days in bed; in the succeeding fourteen months at home on an unrestricted diet including a moderate intake of beer and occasional indulgence in hard liquor he had 7 attacks and spent only seven days in bed. I do not believe that anyone knows what to make of such things and it seems to me that at present we can still only proceed upon the basis of the low-purine hypothesis, while hoping ardently that someone soon solves this riddle for us.

Combating Obesity.—We cannot attack the problem as we would ordinarily do in obseity, *i.e.*, by greatly restricting carbohydrate and fat consumption, because this necessitates the allowing of an amount of protein which forces the taking of more of the purine-containing fowl, fish and meats than is permissible. Therefore we can combat obesity in gout only by a constantly reiterated counsel of abstemiousness. Gouty individuals usually adore stuffing themselves; the attempt should always be made (and it will nearly always fail) to make them leave the table a little hungry still.

Alcohol Restriction.—We like to believe that it is the heavy drinker or the

debauchee who is most prone to gout, and therefore counsel against the "spree," but as a matter of fact few drunkards develop the disease. It is the more or less steady but quite moderate drinker, especially of red wines and beer, who is apt to be gouty. For this reason total abstinence is the thing to be recommended, though I must add that Bauer and Klemperer (1944) have recently reiterated the feeling of their group that the instrumentality of alcohol in precipitating gouty arthritis is unproved.

The Purine-free Diet.—It is perhaps impossible to devise a truly purine-free diet that would be sustaining because even the common vegetables are not purine-free. But the worst purine formers are fish, fowl and meats; these should be omitted from the diet during most of the time. The total proteins need not be reduced; therefore meat, fowl and fish restriction is compensated by the use of large amounts of milk, eggs, cheese and proteins in vegetable form. It has long been held that coffee, tea and cocoa should be withheld, but I am unable to find any evidence that these beverages do actually act as uric acid precursors. Perhaps this is just one of those things carried along in textbooks without real justification; patients would be immensely relieved if the page were torn out.

Actual Diet During the Attack.—The patient is oftentimes miserable enough not to wish much food; this offers good opportunity for a little reduction in his weight. Have him drink all the water possible and permit him to partake only of the following (in small quantities): milk, milk toast with a little butter and sugar, the breakfast cereals (except oatmeal), potatoes and fruits.

Actual Diet in Chronic Gout.—To accomplish the prescribing of a purine-free diet as nearly as is practicable, the patient may be permitted to eat the normal diet for an adult (but in restricted quantities!) provided that the following articles are *omitted:*

All meats, fish and shellfish, and fowl.

Soups: since nearly all soup stocks are made from meat.

Vegetables: asparagus, kohlrabi, lentils, mushrooms, onions, peas, radishes, shelled beans (kidney, lima, navy, soy), spinach and watercress.

Cereals: whole wheat bread, oatmeal, shredded wheat and other breakfast foods made from whole grain.

Condiments: all peppers and spices, catsup, mustard, horseradish and garlic. (Why? Is it just that the condiments increase appetite, or does someone really know that they are more directly harmful?)

Now in order to obtain even reasonable satisfaction on such a diet the patient will have to take inordinate amounts of milk, eggs and cheese—and finally he will rebel. When this occurs allow him an occasional bit of bacon, chicken, or lamb. Among the less harmful fish, Barborka placed haddock, whitefish and fresh salmon. He also placed oysters, crabs and lobsters among the "meaty" things least likely to cause an attack. A small portion of any one of the articles just listed may be given at one meal per day twice a week, and it might be well if the patient could always be held under this much control. Since this rarely happens, one should bear the following things in mind as the diet is expanded:

(*a*) The worst offenders among the meats are sweetbreads, kidneys, liver and brains; among the fish, sardines, herrings, anchovies, pike, cod and perch; among the fowl, squab and turkey.

(*b*) Boiled beef, from which the water has been twice poured off while cooking, has lost some of its purines and thereby becomes more acceptable.

(*c*) Soups are perhaps best not used at all because of their high content in extractives.

(*d*) Adding vegetables from the interdicted list is less harmful than adding meats, fish or fowl.

Relative Amounts of Carbohydrate and Fat.—Bartels (1943) said that indisputable benefit was obtained in 31 of 38 patients in whom fats as well as purine formers were restricted and relatively large quantities of carbohydrates were allowed. Certainly it seems worth while to give this regimen extended trial because Lockie and Hubbard, as mentioned earlier, have shown that fats tend to provoke gouty attacks. Bauer and Klemperer (1944) demur, however, because in their experience gouty attacks were not precipitated with any regularity by a high-fat intake nor did the omission of fat from the diet prove beneficial.

The Cinchophens.—Hench (1941) said that because these drugs are occasionally toxic they should not be used until others have been tried and have failed but he is definitely convinced that they are the most effective of the lot and that their use is justified except for patients with hepatic dysfunction, or idiosyncrasy for the drug, or in those unwilling to take the slight risk, but he also advised that certain precautions be taken. Here is the regimen employed by Hench at the Mayo Clinic: (*a*) cinchophen is used in preference to neocinchophen because it is believed to be more effective even though somewhat more disturbing to the gastro-intestinal tract; (*b*) the patient takes 7½ grains (0.5 Gm.) three times daily for three consecutive days each week and continues this indefinitely with only such modifications as seem indicated in the individual case; (*c*) the following "precautions" are observed: patient must ingest 2 liters of fluid and liberal amounts of carbohydrate daily and take enough alkali (15 to 30 grains [1 to 2 Gm.], potassium citrate or 30 to 60 grains [2 to 4 Gm.], sodium bicarbonate three times daily) to prevent renal colic from precipitation of urate stones in an acid urine; patient must also report such unusual symptoms as anorexia, dyspepsia, nausea, loss of weight, pruritus, or jaundice, and upon the appearance of any of these symptoms he must stop taking the drug at once and report for special therapy (carbohydrates intravenously, high carbohydrate diet, vitamin supplements, and so on). Bartels (1943) felt it important to perform liver function tests at intervals during treatment with cinchophen and to stop the use of the drug when the result of the test fell below normal. Rawls (1942) reported that the administration of vitamin K, which is available commercially in the form of the synthetic preparation menadione, appears to lessen the toxic effects of cinchophen on the liver.

A number of years ago Graham reported a patient who had been on such a cinchophen regimen without any special protective measures continuously for a period of six and a half years, and doubtless there are many unrecorded instances in which the medication has been continued for an even longer time. It is possible that the occasional reactions to the drug are upon an allergic basis, *i.e.*, acute yellow atrophy being comparable in these cases to the acute agranulocytosis sometimes caused by amidopyrine. A mild reaction, omitted (but certainly inadvertently) from Hench's list of warning signs, is urticaria (hives); many men feel that when a patient develops an urticarial reaction to the ingestion of a drug he should never again be allowed to take a dose of hat drug.

Many men feel that the danger of serious poisoning with the cinchophens

outweighs the advantages derived from their use, particularly as something can often be accomplished with other drugs and the disease progresses relentlessly despite all medication anyway.

The Salicylates.—Satisfactory damping down of the symptoms is sometimes obtained with aspirin (acetylsalicylic acid). Ludwig *et al.* (1938) employed 60 to 80 grains (4 to 5.3 Gm.) daily for four days out of each week. Jennings (1937) found sodium salicylate, 80 grains (5.3 Gm.) daily with twice the amount of sodium bicarbonate for three or four consecutive days each week, just as effective as cinchophen. Bauer and Klemperer (1944) felt they had demonstrated clearly that results equal to those ascribed to cinchophen can be obtained by the use of salicylates in high dosage and without any inherent risk. Hench (1941) suggested trial of sodium salicylate, 60 grains (4 Gm.), and aminoacetic acid (glycine), 150 grains (10 Gm.), daily three consecutive days each week, basing the proposal on Quick's (1933) report that aminoacetic acid augments the salicylate promotion of uric acid excretion.

Colchicine.—Some men feel that this drug is effective in warding off acute attacks. Talbott and Coombs (1938) followed Cohen's practice of giving 3 tablets of 1/120 grain (0.0005 Gm.) daily for two or three days each week with satisfaction. In several cases in which colchicine had been used in this way for more than two years no toxic symptoms had been observed.

Thiamine Hydrochloride.—Several investigators have been trying large doses of thiamine but it seems to me in studying their papers that nothing of definite value has been added to therapy from this effort as yet. I gained the impression from the reviews of Hench (1941) and of Sodeman (1941) that they were of the same opinion, and more recently Bauer and Klemperer (1944) stated that they had obtained no good results with thiamine.

Miscellaneous Drugs.—It is not proved, indeed not even strongly indicated, by results attained, that the routine use of iodides or alkalis is helpful in the treatment of chronic gout. Long ago it was proved that lithium salts have no value. Acid, however, is indicated if the patient is on a purine-poor diet since such a diet contains an excessive amount of alkali; the U.S.P. dilute hydrochloric acid may be used in a dose of 15 to 30 minims (1 to 2 cc.) after each meal. However, if the patient is taking cinchophen or a salicylate and accompanying it with an alkali to prevent stone formation, the use of acids would of course be absurd.

Smith has shown that there is no increase in uric acid excretion following the commonly recommended dose of live baker's yeast; two, three and five times this dose likewise gave negative results. In his studies, live yeast cells appeared in the feces in large numbers, showing that they were not killed to any great extent in the gastro-intestinal tract. Oppenheimer and Kunkel (1943) were unable to affect the uric acid concentration of the blood through the injection of purified uricase prepared from pig's liver.

The Allergic Approach.—Allergists are beginning to interest themselves in gout and I think it high time. There is nothing as yet to report except that of course they are concerning themselves with the possible allergens in the patient's diet rather than its purine content. It seems to me that any physician might find it worthwhile looking upon his patient as at least potentially allergic (see Food Allergy) until proved otherwise.

Treatment of Ulcerated Tophi.—Hench (1941) said that if tophi break down intermittently and discharge urates for a long period they may be excised in

order to prevent infection. He said that thorough débridement results in prompt healing.

Exercise.—The value of exercise for the gouty individual has been long recognized. Golf is unfortunately the only form of outdoor exercise that many city men can enjoy, but the fact should not be overlooked that for individuals not too corpulent and whose arteries are not yet markedly sclerosed it is distinctly less valuable than the more vigorous forms of exercise. It is sadly true that the streets of our industrial cities are becoming less attractive to the eye and less stimulating to the spirit as year follows year; still a brisk walk is a brisk walk and as such is worth far more to an individual in need of exercise than is a round of golf as played on a crowded city course.

The Spa.—Spa treatment is endeared to us of old, its value lying not in the ingestion of the mineral constituents of the waters but in the taking of so much water itself, plus the other elements of a complete environmental change which render the resorts so valuable in the treatment of many chronic disorders.

Fibrositis

(*Myositis, Muscular Rheumatism*)

This is possibly the most frequently encountered of the rheumatoid disturbances and likely deserves a more dignified position than it has attained in the literature, for there is no doubt about the incapacitating nature of an attack of fibrositis even though it is usually of only brief duration. Among 900 admissions in the arthritis clinic of the Hospital for the Ruptured and Crippled in New York, Traeger (1937) and his associates made this diagnosis in 262 instances, *i.e.*, patients who presented with pain in or about the joints with no external evidences of joint pathology such as swelling, redness, fluid accumulation, muscular atrophy or deformity and without roentgenologic evidence of bone pathology or any laboratory findings of an elucidating nature. Sometimes there also occur deep-seated "fibrositis nodules," but according to both Traeger and Kelchner (1940) these are apparently less characteristic of the malady in the United States than in England. As the term indicates, fibrositis is an inflammatory reaction in the fibrous tissues of the body, and therefore the terms "myositis" and "muscular rheumatism" are misnomers since it is involvement of the interstitial tissues rather than of the parenchymal muscle tissues which causes the symptoms. Since fibrous tissue exists everywhere the possibilities for anatomic distribution in fibrositis are very great, but the pain, tenderness, and muscle stiffness (jelling phenomenon) which characterize it are most frequently encountered in the following forms: lumbago, torticollis or wryneck; an excruciating headache centering in the back of the neck; intermittent attacks of pain in any muscle groups associated or not with unusual use; stiffness or soreness of the joints after long periods of rest; interstitial neuritis in which the pain and tenderness are in the muscles and not along the nerve trunks; bursal fibrositis, which differs from bursitis in not being accompanied by increase in fluid in the bursa and definite limitation of motion; panniculitis, in which there is a loss of the elasticity of the skin, which becomes more adherent to the underlying tissues; fibrositis of the palmar fascia (Dupuytren's contracture). American writers like to include pleurodynia as simply a primary fibrositis but I notice that recent British authors, such for example as Neligan (1939), do not specifically do so; I doubt if those who have

had much experience with the epidemic form of this malady (see Epidemic Pleurodynia) would agree to its inclusion here.

THERAPY

Prognosis is good in these cases in the sense that crippling and deformity are not to be feared, but it is common experience that to relieve a patient in an acute attack, or to shorten the course of a chronic siege, is easier to desire than to accomplish. Despite the venerable antiquity of this entity its therapy is still in a very uncertain state. Writers on the subject launch into discussions of the necessity to eliminate foci of infection, the value of vaccines, histamine iontophoresis, vitamin stuffing (the latest is vitamin E, used in high dosage by Steinberg, 1943), diet, and so on, in short the things are still being advocated here which have elsewhere proved passé (see Rheumatoid Arthritis). Of course the use of salicylates is indicated, but the two remedies which seem to be of greatest value are the old household ones of heat and massage. For methods of applying heat see the article on Rheumatoid Arthritis. Kelchner (1940) stressed the point that though massage should be begun lightly and gently it should be gradually increased until it becomes very vigorous, the idea being, it seems, to break up the fibrous accumulations. Massage should always be preceded by the application of heat, and it is to be expected that in the beginning it will increase the pain. Krusen (1943) said that stretching exercises always should follow massage. Kelchner said that when the pain is definitely localized, simple needling or else the injection of a few cubic centimeters of sterile 2 per cent procaine hydrochloride solution will bring relief; both Kelly (1942), in Australia, and Travell *et al.* (1942), in the United States, reported full restoration of motion and complete remission of pain in a large proportion of their cases in which they infiltrated procaine solution intramuscularly in patients suffering pain in the shoulder region and arm.

Removal to a warm sunny climate is often very helpful to these patients. Traeger shrewdly remarked that perhaps most of the "arthritis" cases cured by a trip to Florida or Arizona are in truth only cases of fibrositis.

RICKETTSIAL INFECTIONS

(*Epidemic Typhus, Endemic Typhus, Rocky Mountain Spotted Fever, Boutonneuse Fever, Tsutsugamushi Fever, Trench Fever, Q Fever, Bullis Fever*)

The rickettsial organisms, so named by da Rocha-Lima in 1916 in honor of the young American bacteriologist, Howard Ricketts, who had probably first observed them and who himself died of typhus fever, remain a puzzling group having some of the characteristics and attributes of both bacteria and viruses. But in recent years sufficient information has been accumulated with regard to them to warrant the present grouping of a number of diseases under the above heading in this book. These diseases have the following characteristics: (1) They are of world-wide distribution and differ somewhat in their symptomatology in different regions, but they are nevertheless sufficiently similar that all the others must be differentially eliminated before making a diagnosis of any one of them. (2) The organisms are conveyed in some instances from man to man and in others from animals to man, an insect being the intermediary

host and vector in all cases. (3) The essential pathology in the rickettsioses consists in necrotizing damage to blood vessels in various portions of the body. (4) The characteristic clinical features of these infections are (*a*) sudden onset with chills, fever, gastro-intestinal symptoms and headache and pains all over the body and great restlessness with often other manifestations of central nervous system involvement; (*b*) the appearance of a rash some time within the first few days; (*c*) relatively few complications; (*d*) death or termination by crisis with few sequelae. An additional interesting feature characterizing these infections is the fact that the serums of patients agglutinate the X strains of *Bacillus proteus* (*Proteus vulgaris*); a positive agglutination of this sort is called the Weil-Felix reaction, a diagnostic aid which will be discussed in more direct connection with the presentation of each of the entities which is to follow.

Classification of these diseases is still somewhat confused (Blumer, 1941, said that more than ninety names have been applied to classical typhus alone), but I think the group can be presented with sufficient clarity under the following heads: epidemic typhus, endemic typhus, Rocky Mountain spotted fever, tsutsugamushi fever or scrub typhus, boutonneuse fever, trench fever, Q fever, Bullis fever. The therapy and prophylaxis of all these entities may be satisfactorily considered simultaneously. It is of interest in passing to note that evidence is accumulating that trachoma is a disease of rickettsial origin and that some observers regard psittacosis (*q.v.*) as a rickettsial rather than a true virus disease, while some students of thromboangiitis obliterans (*q.v.*) feel there is some connection between that disease and typhus.

Epidemic (Classical or "European") Typhus Fever

(*Louse-borne Rickettsial Fever*)

Epidemic typhus fever is an age-old decimator of the dirty majority of mankind, though it was not recognized as a clinical entity until the sixteenth century and was not clearly differentiated from typhoid fever until the middle of the nineteenth century. The causative organism, *Rickettsia prowazeki*, was named for one of da Rocha-Lima's coworkers who, like Ricketts, died of the disease. It is present in the feces of typhus-infected lice and in the vast majority of instances probably gains entrance to the body through the rubbing of this fecal material into abrasions in the skin; however, evidence is slowly accumulating that air-borne material containing dried infected louse feces may sometimes give rise to the infection when inhaled. This form of typhus is in the main a disease of the cooler portions of the earth, but at the present time its definite endemic foci are known to be, according to Dyer (1944), in the highlands of Central and South America, North Africa and some parts of Central and South Africa, in Spain, in parts of France and Germany and in the invaded states of eastern Europe, in Russia, Turkey, Iran and Iraq, in Afghanistan and in China. Practically all the countries of the north temperate zone have had severe visitations of this disease. The typhus years in the United States were 1812, 1830, 1847, 1865, 1881 and 1893; these outbreaks were usually confined to recently arrived immigrants in the seaboard cities, and very probably were mere importations of the disease; Canada had a visitation of this sort in 1847, in which year the death toll among immigrants was over 20,000. All wars, with the exception of our Civil War, have felt the severe ravages of typhus; probably the greatest havoc was wrought during the Thirty Years'

War in the seventeenth century, and next during the Napoleonic campaigns. In War I the French, British and American armies on the western front were practically typhus-free only because the Germans and Austrians were fiercely fighting to keep it away from their front lines, their rear being heavily attacked by it from Russia. Eastern Europe and the Balkans suffered severely during and after the War, 10,000,000 cases being alleged to have occurred in Russia alone in the period 1919–22; the mortality in the epidemics averaged 20 per cent, with a range of 5 to 70 per cent—the number of persons known to have perished in Rumania was nearly one million and estimates place the number at several millions in Russia. This form of typhus is distinctly more prevalent during the winter months; mortality is lowest in children and highest in the aged. The incubation period seems to be from five to fifteen days. An oft-repeated adage, well characterized by Dyer (1941) as "rather tiresome but too truthful" is that the extent of typhus at any given time is a current measure of human wretchedness. Close quarters, malnutrition and cold invite it surely; we know it now to be active again on the Continent but the censorship prevents accurate knowledge of the extent of the epidemics, if any are occurring, in Germany and the occupied countries; certainly no epidemic has ever been more widely publicized than that which occurred in Naples shortly after our capture of that city.

The interesting Brill's disease, an endemic mild variety of typhus existing in the larger northeastern seaboard cities of the United States, is apparently confined to individuals who emigrated from the typhus-ridden regions of southeastern Europe. It has not been possible to detect man-to-man, or flea- or louse-to-man transmission of this disease. Zinsser and his associates were of opinion that these cases are recrudescences of European typhus fever acquired at an earlier time in an endemic Continental focus, an opinion supported by the findings of Plotz (1943) with the new complement-fixation test. It is definitely a mistake to refer to cases of the endemic typhus of our southern states (see below) as Brill's disease, even though the latter does have a seasonal prevalence more like that of endemic than classical epidemic typhus.

The symptomatology of a fulminating case of epidemic typhus is about the following: Usually, with few prodromata, there is a sudden chill and rise of temperature which is accompanied by nausea and vomiting and a headache; sometimes there are aching pains throughout the body also. The rise in temperature is accompanied by a proportional increase in pulse rate and in the severity of the headache, but the gastro-intestinal symptoms disappear early. The temperature often reaches 105° F. (40.5° C.) on the second or third day, to remain with remarkably little daily remission until the close of the attack. Prostration is very great. On the fourth to seventh day a maculopapular rash appears which changes from pink to red, then purplish-brown; it involves usually all of the body but is often very sparse or absent on the face and neck. On reaching full efflorescence, some of the spots become hemorrhagic and purpura appears irregularly. The patient experiences sleeplessness from the beginning, which gives way to wild delirium, and in severe cases the delirium passes into a state of "coma-vigil" in which the sufferer lies in a relaxed position though the body is usually twitching; the eyes are wide open and staring and there is often a low muttering delirium. Oftentimes there is other early evidence of central nervous system involvement such as tinnitus, vertigo and deafness. There is usually a loose cough almost from the beginning. Small areas of spontaneous necrosis of the skin are not rare. The crisis is

reached on the thirteenth to eighteenth day, after which there is a rapid disappearance of all symptoms, though the discoloration following the rash usually fades gradually and convalescence may be very protracted. The two complications chiefly to be feared are secondary bronchopneumonia and thrombosis of the large vessels. The Weil-Felix agglutination test is of not very great value as an early diagnostic aid for the reason that it unfortunately does not become positive until the rash has appeared, and sometimes not even until late in the second week; agglutination with the OX19 strain of *B. proteus*, which is more reliable than the OX2 strain, will differentiate typhus from tsutsugamushi fever but not from Rocky Mountain spotted fever. Dyer (1944) said that the new complement-fixation test, using typhus rickettsias as antigen, becomes positive during the second week and is of value in differentiating typhus from Rocky Mountain spotted fever. The value of the slide agglutination test of Smorodintzeff and Fradkina (1944) remains to be determined.

Endemic (Murine) Typhus Fever

(*Flea-borne Rickettsial Fever*)

This form of typhus, now recognized to be a disease of considerable importance in the United States, differs radically from the classical form of epidemic typhus (see above) in several respects. In the first place, the great reservoir of the disease is not in man but in the common gray wild rat. In the second place, it is not conveyed by the body louse but the rat louse and the rat flea, particularly the oriental rat flea, *Xenopsylla cheopis*, which keeps the disease going in rats and occasionally conveys it to man probably in the same manner in which epidemic typhus is conveyed (see above). In the third place, the disease does not occur in man in large epidemics under conditions of privation and want but remains endemic, the cases at most grouping themselves about locations especially heavily infested with rats, such as shops, groceries, grain depots, warehouses, and at times the lowest class of dwellings. And finally, unlike epidemic typhus, which occurs predominantly in the winter, endemic typhus though occurring throughout the year reaches its very definite peak in the late summer months. Most of the patients are young adult white males and until recently nearly all cases have occurred in small towns and cities, but latterly the incidence has been rising in rural areas, which may be a reflection of the establishment of the disease in some rodent other than the rat; a number of species have been found susceptible in the laboratory and Brigham and Dyer (1938) once trapped an infected field mouse on a farm. Irons *et al.* (1944) also recovered murine typhus from naturally infected *Ctenocephalides felis*, the cat flea, and they mentioned five human cases of typhus which were probably acquired through the agency of such fleas.

Just how long endemic typhus, whose causative organism is *Rickettsia mooseri*, has been prevalent in this country we do not know, but it was first recognized in Georgia by Paullin in 1913 and has been reported with increasing frequency since Maxcy's intensive studies began in 1923. In the ten-year period, 1929–1938, the number of reported cases was 11,427, but Kemp (1939) undoubtedly voiced the consensus in saying that the true number of cases is very likely greater than that reported. Practically all of these cases have occurred in North and South Carolina, Georgia, Florida, Mississippi, Alabama, Louisiana, Texas and southern California, with a few scattered cases in other southern states, most notably Tennessee, and a very few cases indeed else-

where in the country. This distribution is certainly not that of the common rat, and it may not be purely climatic for there is the flea also to consider. *X. cheopis* was originally found only in seaport cities, then it moved inland throughout the middle and deep South. In 1940 Trembley and Bishopp listed the following midwestern states from which it had been reported: Indiana, Iowa, Minnesota, Illinois, Ohio, Tennessee; and in 1941, Ackert *et al.* added the state of Kansas to the list. It is considered likely that as *X. cheopis* increases its territorial invasion, endemic typhus will go along with it; indeed, the reports of Topping and Dyer (1943) and of others showed that it is already occurring in several northern states. While much of the investigative work on endemic typhus has been done in the United States, the disease is now known to occur very widely throughout the world. The entity called "tabardillo" in Mexico is apparently at times endemic typhus and at other times louse-borne epidemic typhus.

The symptomatology, duration and course of endemic typhus are the same as of epidemic typhus (see above), but the attack is much milder and complications rarely occur. The Weil-Felix test is positive with the OX19 strain in endemic as in epidemic typhus, but leukopenia is more often a characteristic of the endemic form of the disease and there has also been developed a helpful murine complement fixation test. In the age of greatest incidence (young adults) mortality is between 1 and 2 per cent; according to Gordon (1940) it is 5 to 7 per cent in those between forty-five and sixty-five years and about 30 per cent in those above sixty-five.

Rocky Mountain Spotted Fever

(*Tick-borne Rickettsial Fever*)

This disease was formerly thought to be peculiar to certain discrete localities in the states traversed by the Rocky Mountains, having its greatest frequency in Idaho and Montana. We now know, however, that it occurs very widely throughout the country; according to Dyer (1944) the only states from which cases have not yet been reported are Maine, New Hampshire, Vermont, Connecticut, Rhode Island, Wisconsin and Michigan, but I believe that Wisconsin should have been omitted from his list, for Pippin *et al.* reported a case from our state in 1943. The disease has also been identified in two provinces of western Canada and in two states in Brazil, being formerly called in the latter country exanthematic typhus; in Colombia too it has been found to be identical with the entity formerly denominated spotted fever of Tobia. According to both Collins (1944) and Florio *et al.* (1944) the mild, nonfatal infection of unknown etiology closely resembling dengue except for the absence of a skin eruption, and known as Colorado tick fever, is not simply a mild form of Rocky Mountain spotted fever. The causative organism of Rocky Mountain spotted fever, *Rickettsia rickettsii* (or probably more properly *Dermacentroxenus rickettsii*) is hereditary in wood ticks in the West where the tick often conveys it to man; in the cases often referred to as the "eastern" type of the disease the common dog tick is the vector. Both the wood and dog ticks are found on a wide variety of animals: horses and mules, rabbits, deer, wildcats, foxes, squirrels, opossums, badgers, porcupines, skunks, coyotes, wolves, hogs, woodchucks and weasels are so far indicted. According to Wolbach (1940) altogether ten ticks are proved or potential vectors and all North American rodents, man, monkeys, and dogs are susceptible to more or less

severe infections. The work of Magalhaes and Rocha (1942) seems to have convicted pet dogs as natural carriers of the disease in Brazil. In the West, the disease occurs most frequently in spring and early summer and its victims are most often men whose occupations or pleasurable pursuits take them into infested country, but cases occur also among women and children of families living in such areas. In the East the season is between April and early September and many of the cases are seen among campers and children, the latter because of their intimate association with dogs. Definitely, then, Rocky Mountain spotted fever is a rural disease.

The incubation period ranges from two to fourteen days in most instances, though Carey (1939) recorded a case in which the tick was removed on the first day of symptoms. Parker (1938), who has had an enviable experience with this disease, said that the shorter the incubation the more likely is the attack to be severe. In average cases, either with or without a prodromal period of vague illness for a few days, the patient comes down with initial chill, high fever, very severe headache and pains all over the body, and extreme restlessness and insomnia. There may be obstinate constipation or diarrhea, distention of the abdomen and vomiting; retention of urine with incontinence occurs at times. Often, according to several observers, there is a definite body odor. Cyanosis is frequently present and sometimes edema of the extremities and face also; the spleen may be enlarged; nosebleed, photophobia, and conjunctival injection, and a dry hacking cough without definite signs in the lungs, frequently occur. Typically, the rash appears on the second to the fourth day. It usually starts on the wrists and ankles, less commonly on the back, and may be preceded by a mottled appearance of the skin. Rose-colored, and beginning in either macular or papular form, it usually spreads rapidly as a macular rash to all parts of the body surface and the buccal and nasal mucosae. At first it disappears on pressure but later it persists and becomes darker and more or less bluish. According to Parker the larger and more scattered the spots are and the brighter their color remains, the better the prognosis; spots which remain pinheads often become rapidly darker and in such cases the rash soon becomes hemorrhagic and more or less confluent and blotchy. Sometimes in milder cases the spots appear in several successive crops. In very severe cases sloughing of dependent portions of the body, such as the external genitalia, may occur and there are evidences of considerable involvement of the central nervous system, such as delirium, convulsions, stupor, coma. The average duration of the fever, usually characterized by morning remissions, in nonfatal cases is two to three weeks, termination being by lysis; convalescence is usually extremely slow. In fulminating cases death may occur before the rash appears; in less rapidly fatal cases the patient dies on the sixth to twelfth day. There is an abortive form of the disease which is usually stormy but with a very quick recovery, and there are other patients who are able to remain ambulatory throughout the attack; the likelihood is great that many subclinical cases also occur. Agglutinins for the OX19 strain, and sometimes for the OX2 strain also, usually appear toward the end of the second week of the disease and therefore the Weil-Felix reaction will not serve to differentiate Rocky Mountain spotted fever from typhus. However, there is a complement fixation test using the rickettsias of spotted fever as antigen, and when the blood of the patient is injected into guinea pigs there results fever, sloughing of the scrotum and death; also, according to Dyer (1944), a higher proportion of the focal lesions in the animal is found in the midbrain.

pons, medulla and cerebellum in Rocky Mountain spotted fever than in typhus. A further helpful sign in making a differential diagnosis is the fact that in Rocky Mountain spotted fever there is usually a leukocytosis whereas in epidemic typhus the count may be normal and in endemic typhus leukopenia is of more frequent occurrence. In a series of 10 cases in children, Cooke (1944) reported a constant and striking shift of the leukocytes to the left, a feature which had not been previously emphasized in this disease. Parker listed the following sequelae: deafness, impaired vision, insomnia, neuroses, diminished endurance, unfavorable progression of degenerative diseases. Brunsting (1939) and Cohen (1940) each reported a single case which relapsed once. A few second infections are on record. Topping's (1943) compilation of case reports revealed a crude fatality rate of 28.1 per cent in the West and 18.4 per cent in the East; but these figures do not reflect the fact that in certain areas, such as the Bitterroot Valley section of Western Montana and certain localities in Washington, Oregon, Idaho and Wyoming, the death rate is extremely high, averaging, according to Parker (1938), 80 per cent for adults and 37.5 per cent for children.

Boutonneuse Fever

(*Marseilles Fever*)

This entity occurs in Portugal, Rumania and the countries around the Mediterranean; South African tick bite fever and the so-called Kenya typhus in East Africa are considered to be closely related to it, the latter according to Dyer (1944) probably being identical with boutonneuse. The disease is transmitted by a dog tick, the organism being *Rickettsia conori*. A primary sore, called the "black spot" because of its necrotic center surrounded by a red areola, is often found at the site of the bite as in tsutsugamushi fever (see below). In its clinical features the disease otherwise closely resembles Rocky Mountain spotted fever, though Dyer said that in the disease as seen in Marseilles and Italy mental disturbance is less severe than in other rickettsial infections. The fatality rate seems to be below 3 per cent. The Weil-Felix reaction with the OX19 strain of *B. proteus* becomes positive late in the disease. Plotz *et al.* (1944) said that boutonneuse fever can be differentiated from Rocky Mountain spotted fever by means of complement-fixation provided purified rickettsial antigens are used.

Tsutsugamushi Fever

(*Mite-borne Rickettsial Fever, Scrub Typhus, Rural Typhus*)

This disease occurs in Japan (where it was first described as "Japanese river fever"), Formosa, the Philippines, Indo-China, British Malaya, the Netherlands Indies, New Guinea, Borneo, Celebes, Ceylon, India, China and possibly Korea and Asiatic Russia. Simmons *et al.* (1944) said that typhus of all kinds is prevalent in Burma and that the existence of mite-borne typhus could also be assumed in Thailand; these authors further stated that the disease under present consideration occurs not only in North Queensland in Australia but also at scattered points along the eastern coast of that continent to as far south as the city of Sidney in New South Wales. Its existence in the Marshall and Caroline Islands is not yet certain. A great reservoir for the disease apparently exists in field mice, rats, voles, bandicoots and bush and swamp fowl. Like Rocky Mountain fever (see above), which it seems

to resemble very much clinically, tsutsugamushi is a rural disease, the latter differing from the former chiefly in the following particulars: (*a*) The causative organism, *Rickettsia nipponica* (*R. orientalis*, *R. akamushi*, *R. tsutsugamushi*) is transmitted by a mite. (*b*) A necrotizing lesion appears at the site of the bite and there is adenitis of the drainage area and sometimes of other areas as well (the exception here is Malayan and Australian rural typhus, in which this lesion is rarely seen, and it is said not always to occur in Formosa either). (*c*) The rash seems often to make its appearance first on the trunk, but in many of the dark-skinned natives in the affected regions it is not possible to make out a rash at all. (*d*) The Weil-Felix reaction with the OXK strain of *B. proteus* used as an antigen is usually positive after the tenth day but only negative reactions are obtained with OX19 and the OX2 strains; hence differentiation between tsutsugamushi and typhus can be made by employment of the Weil-Felix reaction.

Tsutsugamushi fever, which has been known since ancient times in China, according to Farner and Katsampes (1944), came to be a very important entity in the armed forces in the Southwest Pacific area during War II. I have seen a number of reports already from some of our men who have had considerable experience in the disease and in them there is sometimes reference to an incubation period as short as four to seven days, but in the report of the Commission sent out from the Surgeon General's Office to study the matter in the endemic area it was stated (Bulletin of the U. S. Army Medical Department, May, 1944) that the minimum incubation period is about ten days while the maximum period, though unknown, does not appear to be longer than eighteen days after exposure. Mortality varies widely in reported series of cases between 2 and 40 per cent; indeed according to Simmons *et al.* (1944) mortality may be as high as 60 per cent, but I do not believe such mortality has been reported outside of Japan. In the 200 cases seen by Lipman *et al.* (1944) during War II in New Guinea, the mortality rate was 10 per cent. Reinfections are not uncommon but are usually mild. It has been authoritatively stated from the Office of the Surgeon General (Bull. U. S. Army Med. Dept., 84, 21, 1945) that while convalescence from scrub typhus is often prolonged and many patients may for a time present the picture of neurocirculatory asthenia, recovery from the disease is ultimately complete without any residual damage to the heart or other organs. The length and degree of the immunity conferred by an attack have not yet been determined.

Trench Fever

(*Shin-bone Fever*, *Five-day Fever*, *Wolhynian Fever*)

Trench fever is a practically nonfatal but extremely debilitating disease caused by *Rickettsia quintana*, which is transmitted from man to man by the body louse. Graham, of the British Expeditionary Force, first described trench fever as a new disease in 1915, though it probably existed as an unrecognized entity long before that time in various parts of the world; some observers indeed considered it a revival of medieval "sweating sickness." The disease was probably endemic in Russia and Poland and disseminated to all the fighting fronts in War I by the movement of German and Austrian troops. In 1917, Grieveson stated that at one time 60 per cent of all patients in British military hospitals had trench fever. It is an interesting speculation how much sooner that war might have terminated had it been possible quickly to control this

malady. In 1934, Braslawsky, of Kiev, was practically alone in maintaining that trench fever was continuing its endemic existence in certain parts of Eastern Europe, but time has certainly borne him out for it reappeared in the German Army during War II and outbreaks were described in Poland, Russia, Rumania, Italy, France and Belgium. For example, Bernsdorf (1943) said that the problem became a very serious one after February, 1942, but I imagine the situation was got in hand very quickly when the new delousing powders became available. Hurst (1942) offered as rather convincing proof of his contention that the British Army had not brought the disease back into England after War I the fact that the herding of lice-infested people in air-raid shelters during War II did not result in the reappearance of the disease, as it certainly would have done in epidemic form had it been endemic in the country.

After an incubation period of fifteen to twenty-five days, and prodromal symptoms which are not characteristic, the onset is usually sudden, *i.e.*, all of the symptoms have usually developed in twelve to twenty-four hours from the first appearance of any one of them. There is chilliness or rarely a definite chill, prostration of varying intensity, rise of temperature to 103° F. (39° C.) or more, anorexia and sometimes vomiting and sweating, frontal headache and severe pain "behind the eyes," and generalized pain and tenderness in both muscle and bone; the especial severity of this latter symptom in the lower legs, particularly at night, gave the affection its popular name of "shin-bone fever." A macular rash sometimes occurs on chest and abdomen. The course of a particular case is not predictable; sometimes there is but one bout of fever which is over in a few days, or the attacks occur regularly at three- to seven-day intervals, or the case runs a protracted typhoid-like course. The bronchitis present in some cases during War I was not considered to be of serious moment, but we do not know as much as might be desired of the extent of the circulatory involvement during the earlier stages of the attack. Certainly many of the cases of "effort syndrome" of those days were considered to have had their inception in a bout of trench fever, but Hurst (1942) looking back upon his experience, felt that these cases were only to a minor degree a direct result of the toxemia of trench fever and were mainly functional and preventable conditions resulting from too much coddling on the part of over-conscientious medical officers.

According to Dyer (1944) there has been no report of agglutination of any of the X strains of *B. proteus* by serum from patients with trench fever; in other words the Weil-Felix reaction is negative. It is to be hoped that the Germans and Russians will have something new to tell us about this interesting disease after the close of War II.

Q Fever of Australia and America

This is an extremely interesting "new" entity. In 1937, Derrick reported among abattoir workers and dairy farmers in Queensland 9 cases of a disease which resembled mild typhus but differed from it in the absence of a characteristic rash and the consistently negative Weil-Felix test; severe and persistent headache and a comparatively slow pulse rate were outstanding symptoms. Burnet and Freeman showed that the organism, since denominated *Rickettsia burneti*, is the causative agent. It has been established that a reservoir of the disease exists in the bandicoot and that a certain tick is the natural vector among these animals. There are no records of this tick attacking

man (though Smith, 1941, stated it will do so readily in the laboratory) and a history of tick bite has not been a feature of the human infections; however, the affected occupational group has been exposed to animals and inferentially contracted the disease by contact with ticks or fresh tick dejecta. Derrick *et al.* (1942) found cows susceptible to Q fever and also that in the endemic area in Australia natural infection occurs among them. In the United States, Davis and Cox (1938), and others since, isolated from wood ticks in the West the organism which is now called *R. diaporica*. In the same year, Dyer reported an attack of disease in a laboratory worker who had had some contact with this organism; later, this "Nine Mile" fever (so designated from the site in Montana from which the original batch of infected ticks had come) appeared in epidemic form (15 cases) in one of the United States Public Health Service laboratories in Washington, D.C., in a building housing rickettsial studies. In this outbreak, carefully studied by Hornibrook and Nelson (1940), and Dyer, Topping and Bengtson (1940), the presence of central pneumonitis which was revealed only upon roentgen examination provoked interesting speculation regarding the relationship of this disease to cases of "atypical pneumonia" (see Index), but according to Dyer (1944) the rickettsial organism of Q fever has not been recovered from any cases of atypical pneumonia other than those occurring in the above-mentioned outbreaks. Another disease which is likely to make differential diagnosis increasingly difficult in this field is adult toxoplasmosis (see Index); this disease, however, is caused by the organism known as Toxoplasma and is therefore not a rickettsial infection.

Australian and American Q fevers seem actually to be the same entity for it is now known that the causative organisms, *R. burneti* and *R. diaporica*, are identical.

Bullis Fever

In the middle of 1943, Woodland *et al.* reported upon a tick fever occurring in troops who had been on maneuvers at Camp Bullis, Texas, and described it as a "new" endemic disease, after Maxcy of the Army, Topping of the U.S.P.H.S., and Snyder of the Rockefeller Foundation, acting as a special committee of investigation, had thoroughly examined such patients as remained in the hospital and had studied the clinical records of those who had been returned to duty and agreed that the entity was at least a definite one. The onset in most of these cases was abrupt with initial chill or chilliness and a temperature which rose quickly to 102° to 105° F. (38.9° to 40.5° C.). A few of the patients gave a history of prodromal symptoms for a few days prior to the onset and during the attack most of the men complained of severe postorbital and occipital headache; pronounced lassitude, prostration, anorexia and general weakness were noted during the febrile stages of the disease and a few patients were nauseated and vomited. After an average febrile course of five days, with extremes of four to fourteen days, the temperature subsided by lysis. In some of the severe cases a rash sometimes resembling that of German measles and at other times that of typhus appeared but remained only about forty-eight hours. Considerable weight loss was noted in many of the patients and convalescence was protracted in the cases in which the illness had been severe. Respiratory tract involvement did not occur though the throat was usually slightly red, but all of the patients had enlargement of at least one set of lymph glands and commonly general lymphadenopathy; the glands were

in many instances acutely tender and their involvement persisted throughout the acute stage of illness but disappeared rather promptly with the clearing of the other symptoms. A constant laboratory finding was a very pronounced leukopenia occurring on the second or third day and associated with neutropenia; in many instances the leukocyte count was said to have dropped to 3000 or below and one patient had a polymorphonuclear count of only 23 per cent. Weil-Felix tests using X19, X2, and XK antigens were consistently negative, as were indeed the results of the numerous other laboratory studies which were performed. It was thought that the incubation period of the disease was from seven to ten days.

From their laboratory studies of this entity, Livesay and Pillard (1944) concluded tentatively that it is not Rocky Mountain spotted fever, typhus, or Q fever, and that the rickettsia-like bodies which they recovered from lymph nodes of men ill with the disease, and with which they produced symptoms in guinea pigs, are probably the etiological agent causing Bullis fever without the development of a significant Weil-Felix reaction. Anigstein and Bader (1943) apparently produced a similar disease in guinea pigs by injection of an infectious agent recovered from ticks collected in an area around Camp Bullis.

THERAPY OF THE RICKETTSIAL INFECTIONS

Symptomatic Care.—The patient should be given plenty of easily digestible food and much fluid for in many instances he is facing a sledge-hammer type of toxic attack which quickly batters thin his reserve of stored energy. Lipman *et al.* (1944) gave their patients 100 Gm. of protein daily in the form of one quarter pound of beef, supplementing the diet with eggnog made from fresh or powdered eggs and evaporated or powdered milk to which vanilla or chocolate malt was added; eggs were included in the diet daily. The commission investigating tsutsugamushi fever for the Surgeon General's office reported in May, 1944, that hypochloremia has been demonstrated frequently to develop in this disease and that the patient should therefore be given 6 to 8 Gm. of salt daily. The mouth must be kept clean else it becomes very foul and an easy prey to secondary infection; liquor antisepticus of the N.F. is a good preparation to use for the purpose. For treatment of the cough see the article on the Common Cold. All authorities agree that it is usually necessary and advisable to control the insomnia of fulminating attacks by the use of morphine. If this drug is not being used some less powerful analgesic will be indicated to combat the headache: phenacetin (acetphenetidin) in a dose of 5 grains (0.32 Gm.), or acetanilid, 3 grains (0.2 Gm.); either of these may be reinforced by the addition of ½ to 1 grain (0.03–0.06 Gm.) of codeine sulfate and one of the barbiturates, such as phenobarbital, ½ grain (0.03 Gm.). It is sometimes necessary to resort to lumbar puncture to relieve the cerebral symptoms. The cooling sponge bath is of course indicated if there is hyperpyrexia. Martin (1940) well stressed the importance of special care to avoid bed-sores as the skin is very prone to ulcerate and become gangrenous in these affections.

Digitalis.—The use of this drug in the usual manner in patients beginning to show signs of heart failure is recommended by most writers, but Ahlm and Lipshutz (1944), describing a considerable experience in tsutsugamushi fever, stated that in these cases digitalis has no effect on the rate or the rhythm of the heart nor does it affect the outcome in any way. The study of Woodward

and Bland (1944) reemphasized the fact that in epidemic typhus the circulatory collapse is primarily of peripheral origin; they did not find digitalis indicated in any of their 30 very thoroughly studied cases.

Shock Therapy.—Lipman *et al.* (1944) sometimes gave whole blood transfusions when anemia was present in tsutsugamushi fever and blood plasma in large amounts, together with vasomotor stimulants, was routinely used in cases of peripheral vascular failure without congestive heart failure; but the Surgeon General's Commission felt that the use of plasma should be limited to cases having proved hypoproteinemia sufficiently severe to threaten the development of generalized edema. Martin (1940) considered that because of the endarteritis which characterizes the pathology of a rickettsial attack, transfusions should be given only if they seem "imperatively necessary"; Ahlm and Lipshutz (1944) were also of this opinion and felt that if fluids must be given parenterally, hypodermoclysis is the method of choice. However, Harrell *et al.* (1944) felt that because of the vascular lesions, the loss of body fluids and protein is analogous to that in burns and that the administration of saline solution or dextrose without blood or plasma only aggravates rather than corrects the abnormal physiology by washing out further protein.

Antiserum.—Topping (1943) produced an immune serum in rabbits for employment in Rocky Mountain fever cases. In a group of 52 patients treated with this serum there were only 2 deaths, both in males sixty-six and seventy-two years of age, respectively, or a fatality rate of 3.8 per cent as compared to the expected rate of approximately 18.8 per cent. Topping felt that these results were not conclusive mainly because of the relatively small number of cases in the series but that they warranted further employment of this serum. The use of immunized horse serum in epidemic louse-borne typhus was reported in 1941 by Durand and Balozet, and again in 1944 by Wolman, the latter's findings being practically the same as those of the earlier workers. There was no significant difference in the length of the illness in the 220 treated patients as compared with that in the 220 untreated controls; the death rate in the treated patients was 3.6 as compared with 10.9 per cent in the controls, and of the 71 patients who received serum before the seventh day of their illness not one died. This study of Wolman's was a very laudable one since the serum was given to alternate cases in a large group of patients, but it would have been made additionally interesting had he analyzed it from the standpoint of the age groups of his patients since the mortality in typhus is closely related to age. Stevens (1945) thought that the rabbit antiserum which he used on a very small scale in louse-borne typhus in a military hospital in the Middle East probably reduced the toxemia and modified the severity of the course.

Convalescent Serum.—Convalescent serum seems not to be of proved value in any of the rickettsial infections though it has been tried in practically all of them. To be sure, Alwens and Frank (1943), among the numerous Germans reporting on the use of this measure in the treatment of epidemic typhus during War II, claimed that intravenous doses of 100 cc. of convalescent serum given on the first or second day and repeated on the following day immediately control the fever and symptoms for five days or more and that recurring fever can be controlled by two further doses; but the evidence in the body of their paper was so inconclusive that I am very skeptical of the validity of this conclusion.

Sulfonamides.—These agents have been tried in all the rickettsial infec-

tions and have not proved of value in any of them; indeed in many instances they have served only to make the patients more uncomfortable.

Penicillin.—The Commission investigating tsutsugamushi fever for the Surgeon General's Office reported in May, 1944, that penicillin was of no value in that disease. Yeomans *et al.* (1944) tried it in 4 cases of classical louse-borne typhus; it was not possible to decide whether it had value in these cases but the authors felt nevertheless that it might be expected to offer considerable help to a seriously ill patient who would not otherwise survive the extra burden of a bacterial infection superimposed on that of typhus.

Para-aminobenzoic Acid.—Yeomans *et al.* (1944) tried this agent in 20 cases of louse-borne typhus and compared the clinical course of these patients with 44 who were untreated. They felt that when treatment with para-aminobenzoic acid was started in the first week of illness the clinical course of the disease was rendered much less severe and its duration was considerably shortened. The initial dose was 4 to 8 Gm., which was followed in the majority of cases by 2 Gm. every two hours, adjustment being made in fluid intake and urinary output in the attempt to keep the concentration of para-aminobenzoic acid in the blood between 10 and 20 mg. per cent. Early in the study nausea and vomiting were disturbing but it was soon found that the administration of sufficient sodium bicarbonate to keep the urine approximately neutral in reaction very much lessened the occurrence of these symptoms. Therapy continued until the patient's temperature was normal for twenty-four hours. Since the drug tended to cause leukopenia it was felt that a white blood cell count below 3000 should be regarded as a definite contraindication to further administration.

Atabrine and Calcium.—Early in 1942, van Meerendonk, treating cases of epidemic typhus in the German Army, was impressed by the results he obtained through the use of atabrine, but later in the same year in summarizing his results in a group of 225 cases he said that they were rather disappointing; indeed he felt that the symptoms were increased in severity under this therapy. But later he combined the use of atabrine with calcium, the latter being employed because of his belief that low blood calcium bore a definite relationship to the lesions of the vascular and capillary systems, and felt that the symptoms would have been more severe had not this therapy been employed. Atabrine was given in a dosage of $1\frac{1}{2}$ grains (0.1 Gm.) three times daily, and calcium in a dosage of 10 to as much as 40 cc. of calcium gluconate in 20 per cent solution or of 10 per cent solution of calcium chloride, probably intravenously though the fact is not stated, once daily. Unfortunately the number of patients treated by van Meerendonk with the atabrine-calcium combination is not stated and indeed the whole of the evidence in his paper in unconvincing. Donald and Barker (1942) reported the treatment of 21 cases of epidemic typhus in a prison camp in Germany and stated that atabrine was not of value in these cases. In the United States, Freed (1943) reported that he had treated 4 cases of endemic typhus with atabrine and felt that the drug had a prompt and distinctly favorable effect upon his patients.

Neoarsphenamine and Metaphen.—Baker (1943) reported that for a number of years he had been using neoarsphenamine dissolved in aqueous metaphen solution administered intravenously in cases of Rocky Mountain spotted fever. The mixture is prepared by dissolving 0.3 Gm. of neoarsphenamine in 10 cc. of an aqueous 1:1000 metaphen solution, and injections are repeated at three- or four-day intervals for three or four times. Baker felt that the patients treated

with this combination of agents presented less alarming clinical pictures during the course of their illness and that their convalescence was more rapidly established and of shorter duration than patients not so treated; but unfortunately no evidence other than these statements was supplied by Baker in support of his contention. He warned of course that great care should be employed if these drugs are used when there is evidence of severe renal injury.

Collargol.—During War I the Germans reported collargol to be of specific value in the treatment of trench fever. Sweet and Wilmer (1919) also employed this agent with good results in 35 cases in the British Army, but they were hesitant to ascribe all the credit to this therapy in a disease so variable in its course as trench fever. According to Arneth (1942), the agent was being used again by the Germans in War II; it is given in 1 per cent solution, 10 cc. being injected intravenously at two or three-day intervals with care to prevent infiltration of the extravascular tissues; a pronounced febrile reaction follows the injection.

Prophylaxis of the Rickettsial Infections

Protection Against Lice.—This is of importance in epidemic (European) typhus and in trench fever; the measures are those employed in ridding and maintaining the body free of lice, and fortunately nowadays they are highly effective (see Lice in Index).

Protection Against Mites.—This is important in tsutsugamushi fever. Fortunately it was found during War II, according to Simmons (1944), that dimethyl phthalate could be used to impregnate clothing and effectively repel mites. In substantiation of Heaslip (1941), the commission sent out from the Surgeon General's Office to study tsutsugamushi fever stated, in May, 1944, that the maintenance of cleared areas around dwellings is very helpful in keeping down the incidence of the disease; the commission further recommended sleeping on raised floors and that at the earliest time possible after exposure the individual should take a bath with thorough soaping and scrubbing of the skin and should then apply the anti-mite repellent. The standard Army repellent contains indalone, which is most effective against flies, Rutgers 612 against Aedes mosquitoes, and dimethyl phthalate against anopheline mosquitoes and mites; the repellent effect of this mixture is said to last three to eight hours.

Protection Against Rat Fleas.—This is important in endemic typhus, one of the rickettsial diseases with which we are chiefly concerned in the United States, and is largely a matter of educating the public in the affected regions to fight the rat as a dangerous enemy to health. Of course there is no thought of attempting complete eradication of the rat population, but Bowdoin and Boston (1940) found the following measures feasible in their campaign in Georgia: (*a*) educational meetings designed to acquaint the people with the nature of the transmission of the disease; (*b*) removal of rat harborage such as trash, rubbish and old lumber piles, and insistence upon the use of garbage cans with tight-fitting lids; (*c*) a rat-extermination program in areas known to be foci; (*d*) and finally, and most important of all, rat-proofing measures designed to separate rat and man permanently.

Protection Against Ticks.—This is important in Rocky Mountain spotted, Bullis, boutonneuse and Q fevers. Of course, as Parker (1938) well said, the best method of avoiding infection is to stay away from regions known to be heavily tick-infested, but for a large part of the population this is impossible.

Dogs should be frequently deticked; keeping them clipped during the summer will facilitate this, and dusting frequently with flea powder is also helpful. Children associating with dogs or resident in the country, or even playing on vacant brush-grown lots in the city, should have their heads, necks and bodies examined several times daily. The important thing is to get the tick off at once. Remove him with forceps or while wearing gloves because crushing him in the fingers is dangerous. Sometimes in pulling him away the mouth parts remain in the wound site, which is undesirable, therefore some men advise forcing the tick to detach himself by applying ether, benzine, turpentine, or tobacco juice to him. Wilson (1940) described the following simple method of accomplishing the same thing: strike an ordinary household match, shake it out as soon as it flares, and apply the hot head to the rear end of the tick; he will quickly withdraw his beak. Do not apply the flaming match for this will kill the tick before he can withdraw. Apply tincture of iodine to the wound site, preferably boring in a toothpick end saturated with it, or apply a silver nitrate stick.

When tick-infested areas must be visited by men necessarily engaged in outdoor work or by campers, hunters, etc., the following precautions (condensed from Parker's excellent account) must be observed. (*a*) Women as well as men should wear trousers and the tick must be prevented from reaching the bare legs by wearing socks and high boots, leggings, or puttees over the trouser legs. (*b*) A sharp watch must be kept for ticks crawling up the outside of the clothing (rough clothing will slow him but smooth clothing will give him a less secure hold) and the hand should be frequently passed across the back of the neck to feel for ticks that may have reached that first area of exposed skin. (*c*) The entire body and the inside of the clothing should be thoroughly examined at least twice daily. (*d*) Upon retiring remove all clothing and place it far enough away that ticks cannot crawl from it to the bed. (*e*) Ticks tend to gather in the brush along old trails, in sagebrush and in the grassy strips in the middle of little used roads.

Protective Vaccines.—Dyer (1941) well emphasized the point that specific immunization is feasible in diseases transmitted from man to man because such immunization is cumulative, since each protected individual reduces the sources of infection by one; but in diseases in which an animal other than man is the reservoir of the infection this cumulative factor is lacking. Logically, then, in *tsutsugamushi fever*, and *endemic typhus*, in both of which the known rodent reservoir is of great importance, one would not expect much to come of efforts at preventive vaccination. Indeed, it is considered that even if an effective vaccine were available against endemic typhus its use against the disease in our own South would not be practicable because the cases are relatively so few. The incidence of tsutsugamushi fever, however, is very high in certain restricted areas in the tropical Orient, where it certainly became a serious problem for us during War II. Unfortunately, the vaccine with which Kawamura *et al.* (1939) reported successful trials in volunteers seems to have come to nothing, for Dyer (1944) authoritatively stated that no successful vaccine has yet been developed.

In *Rocky Mountain spotted fever*, in which there is also a great animal reservoir, the existence of areas of very high endemicity and virulence in the West has also warranted studies of a vaccine, with the result that two vaccines are now available. The first of these, the so-called Spencer-Parker vaccine, is prepared from infected tick tissues treated with phenol and solution of formal-

dehyde and is dispensed from the United States Public Health Service Laboratory at Hamilton, Montana, and the National Institute of Health, Bethesda, Maryland. Usual dosage is 2 injections of 2 cc. each, given five days apart and repeated each year in individuals resident in endemic areas, though in some areas of exceptionally high case fatality 3 injections have been used. Parker (1941), summarizing the experience of fifteen years with this vaccine, was able to show very definitely that persons vaccinated the same year they become infected with highly virulent strains are sufficiently protected to lessen greatly the severity of the disease and to insure recovery; against less virulent strains full protection apparently sometimes occurs. The greater number of years a person has been vaccinated the greater his protection, children being in any case more protected than adults, it seems. Insufficient data are available upon which to form an opinion of the protective value of this vaccine in the Eastern form of the disease. The second type of vaccine is that prepared from the infected yolk sacs of fertile hens' eggs by the method of Cox; it is commercially available through several of the manufacturing pharmaceutical houses, but unfortunately I am not able to state precisely how effective it has been shown to be. Anigstein *et al.* (1944) suggested that Rocky Mountain spotted fever might be prevented by injecting a minute dose of the serum of specifically immunized rabbits at the sites of presumably infectious tick bites, but Armstrong and Topping (1944) marshalled several cogent arguments against the feasibility of such a procedure as a practical prophylactic measure.

In *epidemic* (*European*) *typhus*, of which man is the sole animal reservoir, much might have been expected from vaccines but it was not until very recently that a sufficiently innocuous preparation became available for mass immunization. Now, as a result of the yolk sac and agar-tissue culture-yolk sac methods employed by Cox, Zinsser, Castaneda and their associates, we have satisfactory methods of immunizing with killed rickettsias. During War II, typhus vaccination was required for all military personnel having opportunity to come in contact with the disease. It was administered in dosage of 1 cc. at intervals of seven to ten days for three injections, a "booster" dose of 1 cc. being thereafter given at intervals of four to six months. According to Long (1944), conditions obtaining in the Army did not permit a well-defined evaluation of the efficacy of this vaccine, though vaccinated troops did operate in areas where the disease is epidemic and very few cases developed; indeed many of the cases which developed were so mild as to require special laboratory studies for their diagnosis.

At present vaccines are not available against *trench*, *boutonneuse*, *Q*, or *Bullis fevers*.

SANDFLY FEVER

(*Three-day Fever, Pappataci Fever*)

This disease, which is caused by a filtrable virus conveyed by the bite of the night-biting sandfly, *Phlebotomus papatasi*, has a very wide distribution in tropical and subtropical regions. It has been reported throughout the Mediterranean basin and the Near East, in Eastern and Central Africa, in parts of southern Russia, India, Burma and China, and it has been claimed to occur, according to the Bulletin of the U. S. Army Medical Department (80, 15, 1944),

in southern Japan, the Ryukyu Islands, in northern Argentina and in other parts of South America. In the Pacific island areas, Phlebotomus has been reported from Port Moresby, Papua and on Manus Island in the Admiralty group. Mumford and Mohr (1944) were of the opinion that there were very dubious records of outbreaks of "three-day fever" on Manus Island and in New Caledonia. The disease is not known to occur in the United States. In the indigenous regions the natives are usually "salted," *i.e.*, relatively immune, but a large proportion of newcomers to an infested region contract the disease. In both Wars I and II it interfered seriously with operations in the Mediterranean basin, the Middle East and the China-Burma-India theaters. Mortality in sandfly fever is nil and complications of any moment occur with extreme rarity, but an attack may nevertheless incapacitate the patient even more than an attack of malaria. The bout is usually characterized by abrupt onset with a fairly high fever, backache, severe joint and muscle pains, stiff neck, headache, pain behind the eyes and on movement of the eyes, sometimes gastrointestinal distress, sometimes pharyngeal congestion and conjunctival congestion accompanied by agonizing photophobia, and a characteristic flush of the face and neck. An actual rash occurs only in a very small proportion of cases, which is an important point differentiating dengue and sandfly fever. According to Sabin *et al.* (1944), who made an extensive study of the disease during War II both in the field and in experimental infections in volunteers, the blood pressure is sometimes low and the pulse rate slow during an attack; these workers also established the fact that although there may or may not be a true leukopenia, a phenomenon constantly encountered is pronounced relative and absolute reduction in the number of segmented neutrophils associated with a simultaneous definite relative and absolute increase in immature neutrophils (chiefly the staff cells). Shee (1942) stated that choking of the optic disks is a sign of some differential importance, but I have seen no confirmation of this observation. The fever usually drops by crisis and the other symptoms abate between the first and eighth days, usually on the third or fourth day, but convalescence may require another ten to fourteen days and the flush often persists for that length of time also. The attack in children seems to differ little from that in adults except that the incidence of diarrhea is higher. In 10 per cent of Cullinan and Whittaker's (1943) cases a short secondary rise in fever occurred usually about the sixth to seventh day and 15 per cent of the patients had two or three attacks at intervals of two or three months. With regard to the matter of reinfection, however, Sabin *et al.* (1944) remarked that it is common experience that groups which have gone through an epidemic and remained in the infected area are immune during subsequent seasons at a time when fresh groups newly arrived are being infected. The incubation period was definitely established in a few of Cullinan and Whittaker's cases as three days.

While no reservoir of this disease in the lower animals has been definitely established, it is a very disconcerting fact that the virus has been demonstrated upon occasion to be able to pass on from generation to generation in the fly. Fortunately, during War II dimethyl phthalate applied to the exposed skin surfaces was found by Philip *et al.* (1944) to be an effective repellent for *P. papatasi.*

THERAPY

There is nothing to describe except to say that analgesics such as phenacetin (acetphenetidin), acetanilid and aspirin (acetylsalicylic acid) may be freely

used during the time the patient is in bed and feeling very miserable. Walker (1940) found the use of an opiate at night occasionally advisable, but Manson-Bahr (1940) wrote of opium as the most valuable drug in treatment. The latter also said that lumbar puncture has relieved the headache—surely this radical measure is not often resorted to. The results of Shortt *et al.* (1940), and of Sabin *et al.* (1944), with preventive inoculations were inconclusive.

SCARLET FEVER

Scarlet fever is an acute infectious disease of which *Streptococcus haemolyticus* of several types is the etiologic agent. The exhaustive epidemiologic studies of Schwentker *et al.* (1943) showed that the types of streptococci which are the most frequent cause of scarlet fever in a community are also most often involved in other streptococcal disease and that they are furthermore those most common among carriers, but these studies revealed also that for any locality at any given time some types of streptococci have outstanding ability to produce disease, including scarlet fever, some appear incapable of causing scarlet fever but are able to produce other streptococcal illnesses, and still others seem to have a general low pathogenicity.

Scarlet fever is very much more common during the first decade of life than during any other period, and though occurring sporadically it has a strong tendency to become epidemic, the seasonal incidence being greatest in the school period of September to June. It is much more often food-borne (milk or milk products) than is diphtheria, but the studies of Schwentker *et al.* (1945) strongly indicated that most cases of streptococcal infection are by direct air-borne transmission from a carrier or patient or less directly by inhalation of the organisms floating in the general reservoir of air. The virulence of the disease varies, mortality among children in the various epidemics being from 1.5 up to as high as 90 per cent; after the eighth year mortality rarely runs above 3 to 4 per cent, and indeed in recent years the death rate has been very low in all age groups in most parts of the world.

The typical case is characterized, after an incubation period of three to eight days, by sudden onset with nausea and vomiting, high fever, sore throat, leukocytosis, general adenopathy and the appearance within twenty-four hours of a generalized, scarlet, maculopapular ("goose flesh") rash on the body and a punctate eruption on the roof of the mouth. The "strawberry" appearance of the tongue is regarded as characteristic of the disease; nosebleed is not uncommon. The temperature and other symptoms usually begin to subside gradually within five to seven days, and a few days after the disappearance of the rash the period of desquamation begins. It is during this period of desquamation, which lasts for several weeks, that the secondary complications are most likely to arise; there are a great many of these but of those most frequently seen the most severe are peritonsillar and retropharyngeal abscess, cellulitis of the neck, sinusitis, otitis media and mastoiditis, nephritis and arthritis.

There are several atypical types of the disease and two definitely recognized malignant types (both fortunately rare nowadays): the fulminating type in which death occurs from acute failure of the heart almost before the symptoms

of the disease have appeared, and the septic type in which the anginal process in the throat quickly involves the nose and the larynx and trachea, with death from sepsis.

A number of years ago the Schultz-Charlton test was introduced as a diagnostic aid in doubtful cases: 0.2 cc. of scarlet fever antitoxin are injected intradermally and the local blanching of the rash at the site of injection is considered diagnostic of the disease. Goldberg and De Hoff (1942) employed a reverse Schultz-Charlton technic as follows: blood is withdrawn on the day the suspect enters the hospital and the serum tested for its ability to blanch a definite scarlet rash on another patient; if it does blanch the rash the patient probably does not have scarlet fever; if the serum does not produce a blanch, further specimens are collected on the fourteenth and twenty-first days and also tested for their blanching power; if the latter serums give a positive blanch test the diagnosis of scarlet fever is established, and if they do not the patient does not have scarlet fever. Goldberg and De Hoff recognized that the latter half of the procedure is of limited practical value since it would only facilitate the making of the diagnosis late in the disease, but they felt that it would help settle many of the heated arguments that arise over problematic cases.

Scarlet fever is one of the diseases of which the great Sydenham (1624–1689) has left a first-hand account, separating it from measles and giving it its present name; its confusion with measles, however, persisted for a long time after his day. Following the period which corresponds roughly with the American War for Independence in the late eighteenth century, scarlet fever spread rapidly over both hemispheres and now occurs all over the world but is extremely rare among natives of Africa and India.

THERAPY

Nursing Care and Diet.—Mild cases of scarlet fever require practically no treatment, though the physician and nurse will often be greatly taxed to keep the child in bed until the danger of delayed complications has passed. Perhaps enforced bed rest of three weeks is ideal but in the 85 per cent or more of extremely mild cases seen nowadays this is practically impossible of accomplishment and is usually considered unjustified. Children will usually take large quantities of fluid quite readily if offered in the form of lemonade. Diet is usually maintained in the beginning on the liquid basis, with milk predominating, but the causal relationship of a full diet to nephritis in this disease has not been established. It is now agreed that the more liberal diet has proved the better procedure. After desquamation begins, the patient is much relieved by the application of ordinary petrolatum to which a small amount of phenol has been added, but it is well to keep the proportion of phenol below 0.5 per cent if the entire body is to be anointed; I have seen a case of mild kidney injury presumably caused by one application over the entire skin surface of an ointment containing 2 per cent of phenol. The complications must be treated as such when they make their appearance. Many physicians insist upon the most rigid isolation of the patient and the nurse, and I set down in what follows the measures through which such isolation can be obtained, but it is my feeling that this sort of thing will be accepted as antiquated before long: (*a*) toilet facilities for their exclusive use; (*b*) sleeping quarters for nurse in sickroom, or in room adjoining, which is to be entered by no one else; (*c*) physician to be gowned while in sickroom; (*d*) dishes to be sterilized before they are taken from the room; (*e*) garbage to be placed on fresh newspaper outside room

and immediately bundled and burned by an elderly member of the family; (*f*) all linens to be sterilized in the room before being sent to the laundry.

Antitoxin.—The Council-passed product at present available in the United States is a sterile aqueous solution of antitoxic substances obtained from the blood serum or plasma of a healthy animal which has been immunized against the toxin produced by the streptococcus regarded as causative of scarlet fever. It is given intramuscularly, only in extreme cases intravenously; the dose varies with the different manufacturers. In recent years the early enthusiasm with which the antitoxin was hailed has so considerably waned that the following points I believe now comprise the consensus among conservative, unprejudiced observers:

(*a*) Early administration of antitoxin usually causes subsidence of fever and the disappearance of the rash and other toxic manifestations, but carefully controlled studies do not show that the incidence or severity of the complications is lessened with as great regularity.

(*b*) The likelihood of inducing serum sickness may easily cause a longer illness than would be suffered in the average case without the treatment.

(*c*) Severe reactions to the antitoxin itself were of frequent occurrence with the earlier preparations but with the concentrated antitoxins now on the market they do not occur nearly so often.

During War II, a National Research Council Committee recommended to the Surgeon General that antitoxin be given only in moderately to extremely severe cases, *i.e.*, only in the type of case which is very rarely being seen nowadays.

Convalescent Serum.—In recent years the organization of several municipal centers for the collection, preservation and distribution of pooled human convalescent scarlet fever serum is enabling us to assess its value from the vantage point of practical employment in large numbers of cases. In 1944, the Council on Pharmacy and Chemistry accepted such serum from the following centers: Milwaukee Convalescent Serum Center, Samuel Deutsch Convalescent Serum Center of the Michael Reese Hospital in Chicago and the Philadelphia Serum Exchange of the Children's Hospital in that city. It is now the consensus that convalescent serum is fully as effective as antitoxin in reducing the toxic symptoms in scarlet fever and possibly more effective in preventing complications; in addition, if properly given (see below) sensitization or unfavorable reactions do not occur. Occasionally there is an urticaria-like eruption but not true serum sickness. No blood typing or matching is required. Here in Milwaukee, Fox and Gordon (1944), in a comparison of 1000 serum-treated patients with 1000 treated without serum, found that the mean days of fever duration in the controls were 5.5 and in the serum-treated cases 2.1, the duration of the disease in the controls was 43.5 and in the serum-treated 24.5, the number of deaths in the control group was 20 and in the serum-treated group 17; it should be emphasized in judging these figures that the controls were merely consecutively admitted patients with scarlet fever whereas the serum-treated cases were those sufficiently ill to justify the use of the serum.

Method of Administration.—The serum should be given as early as possible, preferably within the first three days. Usually a single injection is sufficient, if given early in uncomplicated cases, but when severe complications are present the injections may be repeated at twelve- to twenty-four-hour intervals. Fox and Gordon (1944) obtained a satisfactory response to the first dose in 83 per cent of their cases and to a second dose in an additional 8.2 per cent.

The dosage formerly advised by Milwaukee Serum Center was found capable of considerable reduction by Fox and Gordon in their more recent study; see Table 5.

TABLE 5.—DOSES OF HUMAN SCARLET FEVER CONVALESCENT SERUM

	Previous Doses Cc.	Present Doses Cc.
Infants:		
Moderate	20	10–20
Severe	20–40	20–40
Children:		
Moderate	20–40	20–30
Severe	60	30–60
Adults:		
Moderate	40–60	20–40
Severe	80–100	40–80

Intramuscular therapy is satisfactory but the intravenous route is preferable because of the immediate distribution of serum. Warm the serum to body temperature in a water bath (over-heating will coagulate the serum and make it unfit for use). Inject slowly. If using the intravenous route, the syringe should be absolutely chemically clean and sterilized by boiling in distilled water.

McGuinness *et al.* (1943) obtained a good response in 76 per cent of 169 cases treated with lyophilized convalescent serum.

Sulfonamides.—That the sulfonamides do not affect the toxic stage of the disease—*i.e.*, do not lower the fever or shorten its course, or cause a diminution in the rash or an improvement in the sore throat—has now been firmly established by a large number of studies which I shall not utilize space to list here. It is conceded, however, that they are exceedingly valuable in reducing mortality when employed in the treatment of serious complications. But the effect of their use from the beginning of an attack upon the incidence and severity of septic complications is still undecided. Apparently the National Research Council Committee in its report to the Surgeon General, in 1941, considered the value of the drug in averting complications to be established, for it recommended that these agents be routinely employed in all cases for "prophylaxis of septic complications." And admittedly there are a number of carefully performed studies in existence which do show the alleged favorable effect. However, the most carefully controlled of all of these studies, that of French (1939), who treated 340 cases at Ruchill Hospital in Glasgow, 170 with and 170 without sulfanilamide, deserves careful consideration. The investigation was divided into two periods, the first comprising July and August and the second January, February, and March, thus avoiding unfair allocation of cases with regard to season. During these periods alternate cases were allotted to the two groups as they were admitted. The general medical treatment was the same in both groups and all patients who upon admission appeared to require antitoxin were given it; of the total lot, 79.1 per cent were given the antitoxin and it happened that they were precisely evenly distributed, 135 in the sulfonamide group and 134 in the control group. The drug was given in large doses for four weeks without a break and the patients were under French's personal clinical care throughout the entire period. "The results show that sulfanilamide had no significant effect upon the initial

symptoms of scarlet fever or upon the kind, incidence, or duration of later complications."

If the attempt is to be made to prevent complications with the sulfonamides then they must be used for a full four-week period, just as French did in the above-cited study, for it has long been known that with regard to complications there is a "second danger period" in the third and fourth weeks. Wesselhoeft (1941) did well, it seems to me, in pointing out that such a procedure will considerably increase the cost of medical care in scarlet fever, referring of course not to the purchase price of the drug but to the expert laboratory supervision which experience has taught is necessary when one is prescribing sizable dosage of a sulfonamide over an extended period of time. In short, routine sulfonamide therapy in scarlet fever is likely to convert a home-treated into a hospital-treated disease in private practice.

At the Isolation Hospital in Milwaukee the use of sulfonamide compounds for uncomplicated scarlet fever has been abandoned.

PROPHYLAXIS

Quarantine.—The traditional rule for discharge from quarantine is that the desquamation shall be complete and that there shall be no suppurative discharges from any part of the body; moisture or discharge of any sort from the nose constitutes "discharge" though not obviously suppurative. However, it has long been recognized that the desquamating material is not infectious and that therefore the only purpose served by maintaining quarantine to the end of desquamation is to hold patients in isolation long enough for suppurations to appear. Whether patients whose scarlet fever has been complicated are more dangerous to the community following release than others is at present still a controversial question. The law in many parts of the United States requires quarantine for a minimum of four weeks from date of report, but in some areas this has been modified to two weeks for adults and three weeks for children. Here in Milwaukee the period is three weeks if there are no infectious discharges or the patient is not still suffering from some other infectious complication in which discharge is not a feature; exposed contacts are kept in quarantine for one week.

A number of men are in opposition to present quarantine regulations and feel that when a child recovers as rapidly as is frequently the case nowadays there is no reason to hold him so long; Musser (1941) went so far as to call the present regulations ridiculous, and I gathered the impression from his paper that he would be satisfied to discharge any patient in a week if he were completely recovered in that time.

Convalescent Serum.—There is such agreement regarding the efficacy of human scarlet fever convalescent serum in preventing or greatly modifying the disease that it will perhaps suffice for me merely to cite our own experience here in Milwaukee. Dr. Maurice Hardgrove, Director of the Milwaukee Serum Center, reported in 1938 that of 1061 individuals exposed to scarlet fever and given protective convalescent serum only 20 (1.88 per cent) developed the disease within fourteen days, while the office of the City Health Commissioner stated that 13.55 per cent of the unprotected contacts in the city were developing the disease within this time during the same period. The Center recommends as prophylactic dosage 10 cc. for infants and young children and 20 cc. for older children and adults. The injection is given intramuscularly and should be repeated every ten to fourteen days in patients having successive exposures.

Neither sensitization nor serious reactions need be feared, but very mild reactions occurred in about 1 per cent of Hardgrove's cases: slight transient elevations in temperature, occasional urticaria, and joint pains lasting but a few days.

Immunization with Toxin.—This method comprises the use of the Dick intracutaneous test for susceptibility and the subsequent active immunization of "positive" individuals by the injection of multiple doses of the Dick toxin.

The Dick Test.—Inject 1 skin test dose of Scarlet Fever Streptococcus Toxin (0.1 cc. of the Dick test material as marketed) intracutaneously in the forearm after thoroughly cleansing the area with green soap. Inspect after twenty-two to twenty-four hours. An area of redness and slight infiltration $\frac{1}{3}$ inch or more in diameter indicates susceptibility. Positive reactions fade rapidly and have usually disappeared in forty-eight to seventy-two hours but reactions which have entirely faded at the end of twenty-four hours are regarded as negative. Because of the extreme sensitiveness of the test, the Dicks advise sterilization of the syringe in distilled water and rinsing of syringe and needle with the test solution before making the injection. The statement is made in the 1944 N.N.R. that the toxin diluted for use will retain its potency for at least two months at room temperature.

Immunization.—Five doses of the immunizing toxin are given subcutaneously in alternate arms at weekly intervals. As marketed, these doses contain:

First injection: 650 skin test doses.
Second injection: 2500 skin test doses.
Third injection: 10,000 skin test doses.
Fourth injection: 30,000 skin test doses.
Fifth injection: 100,000 to 120,000 skin test doses.

Reactions.—Reactions may occur after any of the doses but are most common after the third and fourth; they usually appear in six hours and in most instances have disappeared again in twenty-four hours. The following are the symptoms: nausea, vomiting, fever, scarlatinal rash, sore throat, joint pains, painful cellulitis at the site of injection, occasionally edema and rarely anasarca. Even the staunchest advocates of this method warn against its use in any child in whom one has the least reason to believe, from suggestive symptoms, that scarlet fever infection is already established; and that if a Dick-positive individual has been exposed to scarlet fever one should observe him for two or three days before starting immunization; and that no immunization injection should be made in any individual (exposed or not) until forty-eight hours have elapsed after reading the positive Dick test. It is also considered wise not to immunize children with chorea, rheumatism, heart disease, asthma, eczema and the other allergic ailments. Rhoads and Afremow (1943) noted that young adults in whom immunization is attempted are very likely to develop joint pains if they have previously had rheumatic infections or if they harbor chronic streptococcus infection at the time of the immunization.

Appearance and Duration of Immunity.—As determined by conversion of a Dick "positive" to "negative," immunity may be demonstrated two weeks after the last injection. Some observers believe that temporary immunity of variable duration is conferred upon the majority of children; the Dicks say that probably 90 per cent of those properly injected are permanently immunized.

Status of the Method.—In recent years disagreements with the theoretical bases of this method of immunization and objections to its further trial have

greatly increased in number and force. The following are the chief points made by those who question the value of present methods of Dick testing and immunizing (Bauer; Collis; Earle; Friedman *et al.;* Hobson; Hooker and Follensby; Peterman; Peacock *et al.;* Gordon; Maxcy; Hill):

(1) The Dick toxin, since it does not represent all the strains of streptococci associated with scarlet fever, and since equally toxicogenic strains of streptococci can be recovered from diseases other than scarlet fever, cannot form a valid basis for either a theoretically justifiable "test" or "immunization."

(2) Practical justification of the test has failed to be established, since scarlet fever, frequently in a malignant form, has developed in Dick-test-negative individuals. Furthermore, a large proportion of positive reactions is obtained in individuals known to have had a bona fide attack of scarlet fever.

(3) Most bacteriologists insist that it is not possible to induce complete active immunity against any streptococcus.

(4) The Dick test is much too difficult to read to be of practical use.

(5) Attempted immunization prevents only the appearance of the rash, thus robbing the physician of the most valuable sign of scarlet fever and preventing the isolation of these patients who have scarlet fever without rash.

(6) Even granting that "immunization" really immunizes, only the principal protagonists of the method claim that the immunity is a lasting one.

(7) The reactions to immunization are often so severe that the patient is more ill than he would be with the naturally acquired disease.

Sulfonamides.—In a Naval Station in which there developed a high incidence of streptococcal infections during War II, Coburn (1944) reported that the scarlet fever admission rate of 171 per 1000 strength fell weekly to 70, to 45 and to 0 during the third week following the institution of the daily taking of 15 grains (1 Gm.) of sulfadiazine; it was shown in Coburn's report that such a fall was not to have been expected from previous experience. Watson *et al.* (1943) reported a similar study in the Navy in a group in which the number of cases had reached a level of 10 a week at the time of the institution of sulfadiazine prophylaxis and then dropped to 4 cases a week within the first week of use of the drug and then only a total of 5 new cases appeared among the group during the next three weeks. Similar striking effects were also obtained in the Army study reported by Hodges (1944). So it is apparent that under conditions such as obtain in the armed forces the use of sulfadiazine in small dosage can be highly protective against scarlet fever; but it is unlikely that we can make much use of such a measure in ordinary civilian practice for the reason that situations presenting the epidemiologic conditions of military life do not often arise in civilian groups.

SEPSIS

(*Septicemia*)

Following the example of Herrick and the frequent Continental usage, I employ the term "sepsis" for the description of a syndrome which it is more usual to designate "septicemia" in the United States. This departure is made for the reason that the term "septicemia" places too great stress upon the presence of the causative organism in the blood stream and tends to foster

the misconception that this disease entity is characterized by a state of affairs in which large numbers of the organisms are constantly floating about and multiplying in the circulating fluids of the body. To be sure, eruption of the causative micro-organism into the blood stream, and perhaps a succession of such eruptions, is a *sine qua non* for the development of sepsis, but the mere presence therein of these organisms is not in itself enough to justify the diagnosis—as witness typhoid fever, in which there is a more or less persistent bacteremia, despite which we do not refer to the case as one of "septicemia." From first to last sepsis is a clinically recognizable entity, which has at some time in its course the laboratory-demonstrable feature of organisms in the blood stream; but, as Churchman so well pointed out, it is not the fact of their presence there that is of importance but rather that they have come from somewhere and are going somewhere else. The really serious fact therefore is that a barrier has given way and enabled a local disease to become general.

Most cases of sepsis follow a surgical operation, an abortion or childbirth, an acute or chronic sinus infection or an infection of the same sort in the male genitals or the female pelvis, a sore throat, otitis media, a boil or carbuncle, a compound fracture, or a serious or even a very trivial injury in which the skin is broken; in a minority of cases the original nidus cannot be located. About two thirds of the cases are due to the streptococcus, principally the beta-hemolytic streptococcus, with probably half this number caused by *Staphylococcus aureus*, and the remainder by *Neisseria intracellularis* (meningococcus), *Clostridium welchii* (gas bacillus), *Hemophilus influenzae* (influenza bacillus), *Diplococcus pneumoniae* (pneumococcus), *Escherichia coli* (colon bacillus), and in quite rare instances *Listerella monocytogenes*, *Salmonella choleraesuis* (*S. suipestifer*), *Bacteroides funduliformis* and a few others. The onset is usually sudden, with chill and high rise of temperature (the type of which varies somewhat with the organism involved) and rapid pulse and respiration, sweats, frequently gastro-intestinal symptoms, leukocytosis, multiform skin lesions and a nervous involvement which varies between the extremes of wild delirium and coma. What metastatic involvements are to supervene cannot be predicted in the beginning; meningitis, endocarditis, suppurative arthritis and embolic phenomena are among those that most frequently occur. Some patients die very quickly from an overwhelming toxemia, others linger only to succumb after several weeks or even months. In the days before the advent of the sulfonamides, Tileston placed the general mortality at 60 to 80 per cent, Herrick at 70 to 90 per cent; the latter stated that if one eliminated cases with meningitis, endocarditis, general peritonitis or pylephlebitis (all of which were almost uniformly fatal) the average death rate was only 50 per cent.

It was principally sepsis, of course, that made the hospitals of old the shambles that they were. Even as recently as the eighteenth century physicians declined hospital service "as equivalent to a sentence of death." Reforms followed the independent reports, in 1777 to 1789, of Tenon with regard to the deplorable state of affairs in the Hôtel Dieu in Paris, and John Howard on numerous institutions on the Continent. However, real cleanliness only came into effect after Florence Nightingale began her labors in 1854. Lister, in 1867, inaugurated the era of surgical antisepsis which finally led to the aseptic technic. And now at long last the specific chemotherapeutic agents have effected a considerable change in the results attainable in treating the disease.

THERAPY

Sulfonamides.—The undoubted efficacy of this group of drugs in sepsis is not likely ever to be proved in a controlled series in which alternate cases are handled with and without the drug as they come, the reason being of course that justification for withholding so important an agent in a malady so fatal as this could not be found. However, a near approach to such a study was published by Herrell and Brown (1941) of the Mayo Clinic, who reviewed the results in a series of cases treated in a two-year period after the use of the sulfonamides became general with a nonsulfonamide series treated in the preceding two years. Confining themselves to cases caused only by a hemolytic streptococcus, *Streptococcus viridans* (but not including subacute bacterial endocarditis), *Staphylococcus aureus*, the pneumococcus and the colon bacillus, because the numbers of other cases were too small to be of significance, they had 103 treated cases to compare with 171 untreated cases. It was concluded that the recovery rate was about doubled in general but that this does not represent the best that can be attained for the reason that in the cases most frequently encountered, namely those caused by hemolytic streptococci and *Staphylococcus aureus*, the results were uniformly much better than this. They found also that the three factors of greatest prognostic significance prior to the advent of sulfonamide therapy—the age of the patient, the colony count on initial blood culture and the maximal leukocyte count—had lost this significance, as indicated in the following: (*a*) among patients more than fifty years of age, in whom mortality was previously highest, the recovery rate was increased sixfold; (*b*) approximately as many patients recovered whether the initial colony count was high or low; (*c*) maximal leukocyte count did not substantially affect the recovery rate. A fact which adds to the significance of this report of Herrell and Brown is that it dealt with patients treated only with sulfanilamide and sulfapyridine and toward the end of the study some sulfamethylthiazole—but not sulfathiazole or sulfadiazine for these were not yet in clinical use.

Choice of Drug.—Experience has in general confirmed the superiority of sulfadiazine because its efficacy is fully as great as that of any of the other sulfonamides and its toxicity is probably lower. In 1943, Long said that a recent survey of the occurrence of the important toxic reactions (fever, rash, acute hemolytic anemia, leukopenia, acute agranulocytosis, renal complications and hepatitis) of sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine showed that a total of 11.9 per cent of such reactions occurred in the course of sulfanilamide therapy, 15.9 per cent when sulfapyridine was employed, 18.6 per cent if sulfathiazole was used, and but 6.5 per cent if the drug employed was sulfadiazine. To be sure, since Long's report several other drugs have been studied, most notably sulfamerazine, sulfapyrazine and sulfamethazine, but it does not seem to me that any of these drugs has been shown to be unequivocally superior to sulfadiazine. It is true that sulfamerazine seems to be clinically effective in dosage one half to one third smaller than that of sulfadiazine, but Plummer (1944) was of the opinion that each of these three newer agents shows in some instances a sufficiently high degree of acetylation with a corresponding decrease in the free (active) portion for the treatment on this basis to become neffective. Definite advantages of sulfadiazine are its consistently low acetylation and the great solubility of both its free and acetylated forms; indeed acetylsulfadiazine is the most soluble of the acetyl derivatives of any of the currently used sulfonamides, being, for ex-

ample, eighteen times as soluble in a slightly alkaline urine as acetylsulfathiazole, about three times as soluble as acetylsulfapyrazine, about twice as soluble as acetylsulfamethazine and nearly twice as soluble as acetylsulfamerazine. Anderson *et al.* (1944) found that sulfamerazine had a greater tendency to produce leukopenia and to cause drug rashes and drug fevers than sulfadiazine.

Method of Administration by Mouth.—Usual practice is to administer 60 grains (4 Gm.) of sulfadiazine as an initial dose and then follow this by 15 grains (1 Gm.) every four hours day and night, and perhaps later every six hours, until the temperature has been normal for at least a week. The drug may be administered to infants and young children by crushing the tablet in a small quantity of water and feeding with a spoon. The doses of sulfamerazine may be spaced somewhat wider than those of sulfadiazine. Sulfonamide administration should be accompanied by an adequate fluid intake (3000 to 4000 cc. in an adult) and by the use of alkalis in sufficient quantity to maintain an alkaline reaction of the urine; for the latter purpose 90 grains (6 Gm.) of sodium bicarbonate has been recommended as an initial dose and 40 grains (2.5 Gm.) of the same agent every four hours as the dosage for adults except when nephritis or other contraindicating disease is present. Ohnysty and Wolfson (1944) found it advisable to substitute potassium bicarbonate for sodium bicarbonate when the complicating presence of severe heart damage made it seem unwise to administer the water-retaining sodium ion. In giving alkali, it should be remembered that what is required is not just an arbitrary amount of alkali daily but the administration of sufficient in each case to maintain the urine definitely alkaline. It is desirable to maintain a urinary output of at least 1200 to 1500 cc. per day, but of course one should exercise considerable caution in the administration of fluid to patients with heart disease. When sulfadiazine is given in an initial large dose as above stated, the level of the drug in the blood stream reaches 4 to 6 mg. per cent in four to six hours but thereafter begins to diminish, hence the necessity to repeat the administration at four-hour intervals. It seems to be the consensus that a blood level of between 5 and 10 mg. per cent is desirable to obtain best results, and the above dosage scheme is devised to maintain such a level.

Long (1943) said that sulfonamide dosage for children should be adjusted according to the weight of the child in comparison with the adult dose; a rule-of-thumb dosage for children, as stated by Janeway (1943), is an initial dose of $\frac{3}{4}$ grain (45 mg.) per pound body weight, and then 1 grain (60 mg.) per day per pound divided into four or six doses whichever is most convenient.

Other Methods of Administration.—Where the patient is seriously ill, or unable to swallow, or if he is vomiting, it may be desirable to substitute for the initial oral dose an intravenous dose consisting of 75 grains (5 Gm.) of the sodium salts of sulfadiazine or sulfathiazole, or 60 grains (4 Gm.) of sodium sulfamerazine, dissolved in a liter of physiologic saline solution. The statement is frequently made that the drug should not be dissolved in a dextrose solution nor be given in blood transfusion, the opinion being of course that under these circumstances solubility is slower; as a matter of fact I have not seen any proof that this is the case, but until the matter is settled it certainly seems a wise and easy precaution to administer the drugs only in physiologic saline solution. Of course it is necessary to obtain an alkaline urine under these circumstances also; Plummer (1944) said that when using sodium sulfadiazine parenterally he uses sixth molar sodium lactate solution about 1000 cc. daily.

The advantage of attempting to prevent renal reactions through alkalinization rather than relying exclusively on giving a high fluid intake will be apparent when it is stated that increasing the fluid intake two fold can only double the amount of acetylsulfadiazine dissolved, whereas raising the urine from acid to alkaline in reaction will increase the solubility of the acetylated product more than twenty-five times.

Taplin *et al.* (1943) stated that sodium sulfadiazine and sodium sulfathiazole may be given satisfactorily by hypodermoclysis in the form of 0.5 per cent solution in physiologic saline solution. The sodium sulfonamides may be added to the vehicle and the mixture then heated to the boiling point and allowed to cool to body temperature before administration. It was found that with sodium sulfadiazine the maximum concentrations in the blood were reached in four to eight hours after administration was started and that the optimum time for giving a second hypodermoclysis was twenty to thirty hours after the first had been started. Sulfanilamide may also be given by hypodermoclysis; bring a measured quantity of physiologic saline solution or sixth molar sodium lactate solution to a boil, cut off the flame, add enough crystalline sulfanilamide to make a 1 per cent solution, and shake gently until the drug dissolves; then allow to cool to body temperature before starting the hypodermoclysis. Sulfanilamide may not be given intravenously or intramuscularly. Hall *et al.* (1942) said that 6 cc. of a $33\frac{1}{3}$ per cent solution of the sodium sulfonamides may be safely given intramuscularly without the production of necrotic sloughs provided one uses a long needle and deposits the entire dose into the muscle; I imagine not many men care to take a chance with these injections.

The studies of Turell *et al.* (1940), and Strauss *et al.* (1941), indicated fairly good absorption of sulfanilamide from the rectum. Wood (1941) recommended the following practice: keep on hand a solution of sulfanilamide saturated at room temperature, which amounts to approximately 4 grains to the ounce (0.25 Gm. per 32 cc.), and then add the desired quantity of this to a dextrose-saline solution and administer four-hourly as a retention enema. Mackenzie (1943) found that sulfanilamide is poorly absorbed from suppositories. None of the other sulfonamides is well absorbed from the rectum either when given in solution or suppository form.

Sulfonamide Toxicity, Resistance, etc.—See the separate chapter on this subject at the end of the book.

Penicillin.—At the time of writing it is still not possible to present a very satisfactory account of the place of penicillin in the treatment of sepsis for the the following reasons. (*a*) the very restricted amounts of the agent available for use in civilian practice until very recently made it mandatory that it be employed only in seriously ill, often in nearly moribund, patients; (*b*) not enough time has yet elapsed since the relaxation of the restrictions upon its distribution to civilian hospitals to have permitted the preparation of any reports of its very extensive employment; and (*c*) the men in the armed services who are still having the largest experience with penicillin are in the main too busy employing the agent to take time out for a description of their accomplishments with it. The following is therefore the best that I have been able to put together at this time.

Indications and Contraindications.—In the middle of 1944, the Council on Pharmacy and Chemistry of the American Medical Association published the following two lists of infections in which penicillin is and is not effectively employed:

EFFECTIVE IN

All *staphylococcic infections* with and without bacteremia:
- Acute osteomyelitis
- Carbuncles—soft tissue abscesses
- Meningitis
- Cavernous or lateral sinus thrombosis
- Pneumonia—empyema
- Carbuncle of kidney
- Wound infections

All cases of *clostridial infections:*
- Gas gangrene
- Malignant edema

All *hemolytic streptococcic infections* with bacteremia and all serious local infections:
- Cellulitis
- Mastoiditis with intracranial complications, *i.e.* meningitis, sinus thrombosis, etc.
- Pneumonia and empyema
- Puerperal sepsis
- Peritonitis

All *anaerobic streptococcic infections:*
- Puerperal sepsis

All *pneumococcic infections* of
- Meninges
- Pleura
- Endocardium

All cases of sulfonamide-resistant pneumococcic pneumonia

All gonococcic infections complicated by
- Arthritis
- Ophthalmia
- Endocarditis
- Peritonitis
- Epididymitis

Also all cases of sulfonamide-resistant gonorrhea

All meningococcic infections not responding to the sulfonamides

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NOT ESTABLISHED AS EFFECTIVE FOR

All gram-negative bacillary infections:
- Typhoid—Paratyphoid
- Dysentery
- Escherichia coli
- Haemophilus influenzae
- Proteus vulgaris
- Bacillus pyocyaneus
- Brucella melitensis (undulant fever)
- Tularemia
- Friedländer's bacillus

Tuberculosis

Toxoplasmosis

Histoplasmosis

Acute rheumatic fever

Lupus erythematosis disseminatus

Infectious mononucleosis

Pemphigus

Hodgkin's disease

Acute and chronic leukemia

Ulcerative colitis

Coccidioidomycosis

Malaria

Poliomyelitis

Blastomycosis

Nonspecific iritis and uveitis

Moniliasis

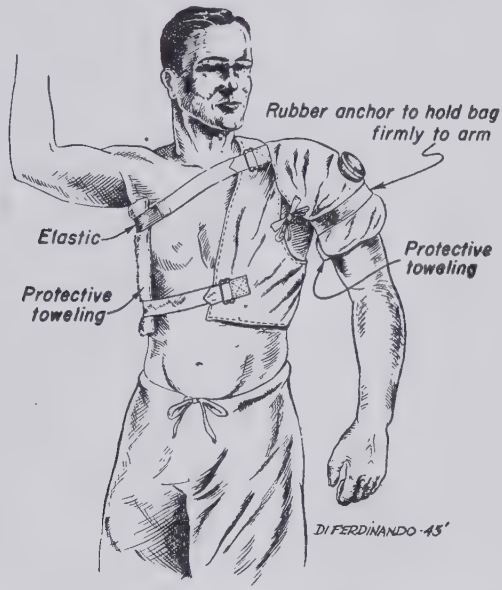
Some of these infections are dealt with elsewhere in the book and the use of penicillin in their treatment is there described: pneumonia, cerebrospinal meningitis, syphilis, gonorrhea, gas gangrene, and so on. In the group of infections with which we are more specifically concerned here in the subject of sepsis, it seems that penicillin has achieved its greatest triumph in cases of staphylococcal septicemia, septicemia or meningitis due to a sulfonamide-resistant streptococcus or pneumococcus, in cases of sepsis in sulfonamide-sensitive individuals, and in cases of osteomyelitis of the facial bones, in which latter condition Kirby and Hepp (1944) recently showed it to be far more effective than the sulfonamides in preventing the dreaded extension of the infectious process into the brain and meninges. The reader must realize, however, that penicillin is strictly selective in its antibacterial activity; an interesting case in point was that reported by Nichols and Herrell (1944) whose patient had extensive cellulitis of the arm complicated by staphylococcic septicemia and pneumonia, and who during the time she was responding splendidly to penicillin therapy developed a urinary tract *Escherichia coli* infection which persisted until sulfathiazole was administered.

Intramuscular Administration.—The most usually employed procedure is to inject one eighth of the total twenty-four-hour dose deep into a gluteal or other

muscle every three hours day and night. When so injected penicillin reaches its maximum titer in the blood stream within fifteen minutes, but half of it is gone within the next fifteen minutes and the titer has fallen to one-fourth the maximum by the end of an hour and to zero by the end of two hours. The method is nevertheless preferred by most men for the reason that it is considered that the disturbance of the patient every three hours, the jabbing with a needle at these frequent intervals, and the pain which oftentimes follows these injections are not as objectionable features as the thrombophlebitis which seems frequently to follow the use of penicillin intravenously; this latter matter will be discussed in a moment. Armstrong *et al.* (1945) felt that penicillin action is more prolonged if it is administered intramuscularly in 5 per cent dextrose instead of the usual physiologic salt solution. Romansky and Rittman (1944), at the Walter Reed General Hospital, studied the prolongation of the presence of penicillin in the blood stream after intramuscular injection by incorporating it in a mixture of beeswax and peanut oil; their report of the use of such a preparation in a very small number of patients was sufficiently encouraging to warrant further study, and Zinnamon and Seeberg (1945) confirmed the findings also in a small number of cases. Parkins *et al.* (1945) reported prolongation of penicillin effect following intramuscular injection in vehicles containing 6 to 20 per cent ossein gelatin and a long-acting vasoconstrictor drug. Trumper and Hutter (1944) chill the site of injection by application of an 80-ounce ice-bag 90 per cent filled with crushed ice and the air squeezed out to insure easy molding. Beginning the applications two hours before the first injection and replacing the bag of melted ice every few hours by a fresh one renders the injections painless and insures satisfactory bacteriostatic levels of penicillin though the twenty-four-hour dose is divided among only three instead of the usual eight injections. The penicillin solution is placed in ice for at least five minutes before injection, a ½-inch needle (three-quarters inch for the obese) is employed, and alternating deltoid muscles are used daily; it would not seem feasible to employ the chilling method for a protracted period in cases of pneumonia, thyroid or thoracic surgery. Continuous intramuscular infusion has also been employed, using the preparation just as prepared for continuous intravenous infusion, but then employing an intramuscular clysis needle introduced deeply into the muscles on the inner or outer side of the thigh and allowing the solution to run in by a drip method as an intramuscular clysis. Harris (1944) described the clinical results obtained with this method as "eminently satisfactory" in 25 cases in which it had been employed, the usual rate of flow being between 12 and 15 drops per minute or approximately 50 cc. per hour. Morgan *et al.* (1944) found the advantages of this method to be: (*a*) continuous maintenance of adequate blood titer; (*b*) comparative freedom from pain; (*c*) availability of numerous sites for transfusion, poor musculature being apparently no bar to the employment of the method. They found, however, that the disadvantages are: (*a*) a tendency to local infection and abscess formation around the site of the needle introduction; (*b*) the possibility of having to restrict total fluid intake. It seems that when the continuous intramuscular in fusion method is employed the medium used for solution of penicillin may be dextrose-saline or saline alone.

Intravenous Administration.—When penicillin is injected intravenously the titer in the blood rises very much higher than when it is given intramuscularly but falls even more rapidly than when the latter method is employed. There are few observers, therefore, who feel that the intravenous adminis-

tration of the drug at three-hour intervals is advisable, but the continuous intravenous administration by a drip method is still preferred by some workers, notably Herrell (1944) of the Mayo Clinic, and Bloomfield *et al.* (1944) of Stanford University. The advantage claimed for this method of administration is of course the obvious one that a higher titer of the agent is maintained in the blood stream at all times. It is further felt that many patients are less disturbed by the necessary partial immobilization accompanying the intravenous method than by the trauma, both physical and nervous, of the intramuscular method. As to the matter of thrombosis of veins see the discussion of penicillin reactions below. Two attempts to prolong the action of penicillin when given intravenously have been reported: that of Rammelkamp and Bradley (1943), who simultaneously injected diodrast to reduce renal elimination, and that of Beyer *et al.* (1944), who sought to reduce renal elimination by the simulta-



Supporting harness for ice-bag to prolong penicillin action. (Reproduced through courtesy of Dr. Max Trumper.)

neous administration of sodium para-aminohippurate; it seems to me that both of these methods are still in the experimental stage.

Intrathecal and Intraventricular Administration.—In normal individuals no penicillin is excreted in the cerebrospinal fluid, but when there is meningeal inflammation penicillin can be detected in the spinal fluid in small amounts when given intramuscularly or intravenously. However, the drug may be injected intrathecally and it is often so injected in cases of meningitis. It has also been injected directly into the lateral ventricles; McCune and Evans (1944) found evidence of only minimal passage of penicillin from the spinal canal into the ventricles in two hours and pointed out that the normal hindrance to such passage against the direction of flow of the cerebrospinal fluid is augmented in meningitis when arachnoid adhesions and exudate may partially obstruct the normal spinal fluid pathways.

Oral Administration.—Penicillin had not been effectively administered by

mouth until recently because it is destroyed by the hydrochloric acid of the gastric juice. Attempts to effect its absorption through the employment of enteric-coated tablets or the simultaneous administration of penicillin and sodium bicarbonate have not met with success, but György *et al.* (1945) reported the attainment of satisfactory therapeutic effects in a small group of patients given penicillin by mouth in combination with tridosium citrate, the two agents being used in the proportions of 10,000 units of penicillin to 1 or 2 Gm. of the trisodium citrate. Libby (1945) stated that when a salt of penicillin is dispersed in cottonseed oil and dispensed in gelatin capsules made up to contain either 10,000, 25,000 or 50,000 units per capsule, a penicillin blood titer within the therapeutic range may be maintained over an eight-hour period by the oral administration in a single dose of approximately 90,000 units of the drug. McDermott *et al.* (1945) also found that the duration of the serum concentration after oral administration can be much prolonged by incorporation of penicillin in oil or oil and wax, and they felt that the present problem of greatest importance in oral administration is to find the ideal vehicle to assure maximum prolongation. Further developments in the field of oral administration will be awaited with great eagerness.

Dosage.—The dosage of penicillin is by no means standardized as yet, but some such schedule as that published by Dawson and Hobby (1944) is probably most frequently followed. *Staphylococcic infections:* (*a*) Chronic osteomyelitis and chronic abscess formation with or without bacteremia, 20,000 units every four hours intramuscularly, duration of treatment to be dependent upon the severity and extent of the process and on the clinical response. (*b*) Acute osteomyelitis, acute abscess formation, acute phlegmonous cellulitis and so on, 10,000–15,000 units every four hours intramuscularly, seven days' treatment or less usually being sufficient. (*c*) Meningitis, 20,000 units locally daily or every two days for 3 or 4 injections and such systemic therapy as is indicated by the nature of the primary infection. *Pneumococcic meningitis*, 20,000 units intrathecally daily, 2 or 3 injections usually being sufficient with systemic therapy as indicated. *Streptococcic infections* due to hemolytic streptococci of the Lancefield group A usually respond to 10,000 units every four hours intramuscularly for four or five days unless the infection is chronic, with or without bone involvement, when prolonged treatment may be necessary; in infections due to other streptococci, 20,000 units every four hours intramuscularly, the duration of therapy being dependent on clinical response. As a guide to dosage in children, we have the record of the case of Litvak *et al.* (1944) who saved the life of their nearly moribund infant of six months with pneumococcic meningitis by the intrathecal injection twice daily of 5000 units and the intramuscular injection every three hours of 2500 units. In their case above referred to, McCune and Evans injected 7500 units in 5 cc. of saline solution into the ventricles. Cairns *et al.* (1944) injected only 3000 to 4000 units daily in 4 to 10 cc. of solution, 12 of their 16 cases of pneumococcal meningitis so treated recovering. When the continuous intravenous drip method is being employed it is customary to allow the fluid to drip at the rate of 30 to 40 drops per minute, the dosage received by the patient of course depending upon the amount of penicillin that was dissolved in the saline or saline-glucose solution. I think it well to reiterate that Bloomfield *et al.* (1944) found this the preferred method of administration in serious infections, and that in severe staphylococcal infections in an adult they felt that 300,000 to 400,000 units per day should be given until the patient is definitely on the mend, and that a dosage

of 150,000 to 200,000 units a day thereafter should be continued until the patient is well. They also pointed out that in staphylococcic sepsis it is extremely difficult to tell when the patient is cured since bacteria may fail to grow in blood cultures, demonstrable lesions may heal, temperatures may decline or be normal, and still within a few days after treatment is stopped blood cultures will again be positive and lesions will recur, this being especially true when bone is involved.

Toxicity and Reactions.—When using penicillin one does not have any of the worries attendant upon the employment of the sulfonamides or an organic arsenical, for this new agent seems not to be capable of causing damage to the parenchymatous organs—no kidney, liver, bone marrow, or brain damage need be feared, and the only sort of skin reaction induced is urticaria and that seems to be very exceptional; indeed such an eruption was reported in only 14 cases in the group of 500 cases of penicillin-treated infections reviewed by Keefer *et al.* (1943). However, Herrell (1944) said that he had observed urticaria or "irritative" dermatitis twice in 150 cases, that he believed this skin reaction would be observed more frequently as more penicillin is used, and that in his opinion continuing to force penicillin in the presence of urticaria or such a dermatitis might result in the development of an exfoliative dermatitis, although he admitted that at times, as others have reported, one may give penicillin without difficulty to patients who have previously exhibited this reaction. I believe it is now the consensus that the few transitory attacks of various sorts which occasionally accompanied the administration of early lots of penicillin, as well as the occasional chill and fever reaction, were due to impurities in the early preparations; these things are very rarely seen nowadays, though an occasional patient who is being given large doses of penicillin develops diarrhea which is easily controlled by the administration of paregoric. It is also the opinion of many observers that the pain caused upon intramuscular injection and the thrombophlebitis upon intravenous injection are also due to impurities; it is certain that irritation of the veins accompanies the use of penicillin very much less frequently now than it did formerly. Criep's (1944) report of a case of acquired sensitivity to penicillin, the patient having received penicillin on a previous occasion and then developing urticarial reactions shortly after receiving the later injections of penicillin, the urticaria being continuous and universal when the drug was given daily, may be looked upon as either a very unusual occurrence or as simply an indication of the sort of thing we may see rather frequently when penicillin comes to be more universally employed. Very few reactions have been reported following the intrathecal injection of penicillin, but Cairns *et al.* (1944) reported systemic reactions which were usually quite transient after the intraventricular introduction of the agent; the reactions twice elicited in the patient of Johnson and Walker (1945) comprised coma, vascular collapse and clonic spasms and caused these observers to suggest that penicillin be administered intraventricularly only in small amounts and with caution.

Preparation of the Solution.—Penicillin is available in sealed glass ampules of 25,000 and 100,000 units each. It is unstable in the air and hygroscopic, and is to be preserved in the refrigerator until used because in the dry state it is considered to lose its potency rapidly under the influence of heat. The Council of Pharmacy and Chemistry, in 1944, recommended that when large unit sizes are being employed in the hospital, the contents of the ampule be dissolved in water or saline solution so that the final concentration is 5000 units

per cc. and that this solution be stored under aseptic precautions in the icebox and made up freshly every day. At some clinics it has been customary to take no more than 150 cc. of such a solution to the patient's bedside at a time in the feeling that the solution would deteriorate rapidly at room temperature, but Kirby's (1944) studies convinced him that the lots of penicillin now available are much more heat stable than the earlier cruder lots and that a twenty-four-hour supply in saline solution may safely be kept at room temperature; indeed he even felt that it would be safe in temperate climates to mix two or three days' supply, either for intermittent intramuscular injection or for continuous intravenous drip, and leave it at the patient's bedside, and that even in the summer a full day's supply could be left at room temperature with a considerable margin of safety. For intramuscular injection 5000 units of penicillin are customarily dissolved in 1 cc. of isotonic saline solution; for intravenous drip administration 25 to 50 units per cc. are customarily employed.

Resistance.—McKee and Houck (1943), Schmidt and Sesler (1943), Dawson and Hobby (1944), and a few others have reported the acquisition of resistance to penicillin by virulent strains of various organisms, especially staphylococci. Amazingly, however, the development of this state of "fastness" is accompanied by a corresponding loss of virulence in the organism, and furthermore the organism's response to the sulfonamides is not altered when it becomes penicillin-fast. Such instances of penicillin-fastness must be relatively rare events since only one possible instance of the sort was encountered in Dawson and Hobby's series of 100 cases, and Bloomfield *et al.* (1944) in a study of the circumstances under which penicillin fails to yield satisfactory results, opined that the development of penicillin-fastness probably plays a very small part in the causation of such therapeutic failures. The investigation of Todd *et al.* (1945) revealed that, at least under conditions obtaining *in vitro*, the "fastness" of staphylococci to penicillin is not a permanent characteristic.

Combined Sulfonamide and Penicillin Therapy.—Waring and Smith (1944) treated 13 patients with pneumococcic meningitis by combined sulfonamide and penicillin therapy. Of the 13 patients 12 recovered, the single death occurring within ten hours of admission; 3 of the patients had previously failed to respond to penicillin therapy alone. These results were better than they had experienced with sulfonamide alone, with sulfonamide and serum combined or with penicillin alone.

Elimination of Foci.—It is certainly the consensus that the systemic employment of the new chemotherapeutic agents should not preclude attempts to halt the influx of organisms into the blood stream either through the surgical elimination of the primary or secondary foci or through local application of the chemotherapeutic agents. But it seems to me that these matters, like certain other phases of the employment of chemotherapy such as the local use of chemotherapeutic agents in the peritoneal cavity and in the management of osteomyelitis and mastoidectomy wounds and in obstetrical and gynecological practice, all belong in the realm of the surgeon and should properly not be discussed by me here.

Antiserums.—Antistreptococcus serum has been before the profession since 1895 and is still waging a fight to hold what little good opinion it may have gained; lack of evidence of its therapeutic worth in sepsis prevents its acceptance by the Council on Pharmacy and Chemistry of the American Medical Association. There is certainly no convincing report of any greater success with scarlet fever antiserum. Staphylococcus antiserum likewise has practi-

cally nothing to its credit, though some hope was built up a few years ago as a result of Julianelle's (1939) studies with a rabbit serum containing a high titer of precipitins for staphylococcic polysaccharides. Neal *et al.* (1940) reported the use of specific antiserums in most of 30 cases of pneumococcic meningitis and 29 cases of influenza bacillus meningitis with 10 recoveries in the first group and 14 in the second, but they attributed these fine results to the sulfonamides which were also employed. Alexander (1944), however, reported excellent results from the employment of her type B *Hemophilus influenzae* specific rabbit serum in addition to one of the sulfonamides. Sodium sulfadiazine is given subcutaneously in a dosage of 0.1 Gm. per kilogram body weight and then the serum is administered intravenously in dosage dependent upon the concentration of glucose in the spinal fluid prior to the beginning of treatment: *i.e.*, for a spinal fluid sugar under 15 mg. per 100 cc., 100 mg. of antibody nitrogen (150 mg. for a child over three years of age) is given; for a blood sugar of 15 to 25 mg. per 100 cc., 75 mg.; 25 to 40 mg. per 100 cc., 50 mg.; and over 40 mg. per 100 cc., 25 mg. The sulfadiazine is repeated at twelve-hour intervals for at least 2 doses and further dosage is administered by mouth, together with fluids and alkalis, in amounts depending upon the response of the patient. Alexander has treated 87 patients either in the Babies Hospital in New York or under her close supervision in other institutions with this combined sulfonamide and *H. influenzae* serum regime; 78 per cent of the patients have recovered completely.

Other Types of Specific Therapy.—It seems to me that there is no longer any justification for occupying space with a description of the methods of employing bacteriophage, foreign protein therapy and immunotransfusion.

Supportive Care.—Unless it is necessary to rest the bowel, the diet should be as nutritious and full as possible. When nutrition is not being maintained because of inability to retain food in the stomach, the nutritive enema (see Index) should be given consideration. Diluted orange juice or lemonade are pleasing forms in which to administer nourishing fluids by mouth. When the patient is vomiting it is often advisable to discontinue the attempt to supply food and fluid by mouth and to resort to the intravenous administration of dextrose, either occasionally or by the continuous drip method (venoclysis). If the dextrose solution is prepared with physiologic saline or preferably Locke's solution, the loss of chlorides occurring in excessive vomiting is combated; the dextrose is also protective against acidosis. Hypodermoclysis of physiologic saline solution will of course supply fluid and chloride but no nutriment. If the attempt is not being made to have one of the sulfonamides retained when administered by mouth, the introduction of a Levine duodenal tube for continuous drainage (with suction if necessary) of the stomach may be helpful.

SMALLPOX

"Since my Lady Mary Wortley Montagu brought home the custom of inoculation from Turkey (a perilous practice many deem it, and only a useless rushing into the jaws of danger), I think the severity of the smallpox, that dreadful scourge of the world, has somewhat been abated in our part of it; and remember in my time hundreds of the young and beautiful who have been carried to the grave or have only risen from their pillows frightfully scarred

and disfigured by this malady. Many a sweet face hath left its roses on the bed, on which this dreadful and withering blight has laid them. In my early days this pestilence would enter a village and destroy half its inhabitants: at its approach it may well be imagined not only that the beautiful but the strongest were alarmed, and those fled who could. One day, in the year 1694 (I have good reason to remember it), Doctor Tusher ran into Castlewood House, with a face of consternation, saying that the malady had made its appearance at the black-smith's house in the village, and that one of the maids there was down in the smallpox."

—W. M. Thackeray: "The History of Henry Esmond."

Smallpox has doubtless existed since the earliest times in China, India, Africa and the Mediterranean littoral, though there is considerable doubt whether it was described by the Greeks or even the early Romans. Greenwood says that it entered Europe with the Saracens; it did not reach England until the tenth century. Cortez brought it to the western hemisphere (Mexico) shortly after the discovery of the New World. The first medical publication in North America dealt with smallpox (Thacher's "Brief Rule to Guide, etc.," Boston, 1677). According to Russell (1940) the disease did not reach Hawaii until 1853, when it promptly carried off 8 per cent of the population. The malignant "classical" form (variola) still holds ravaging sway in the hinterland of the less enlightened countries, with a mortality of about 25 per cent, and in well vaccinated lands, such as certain of the continental European countries, the rare outbreaks are of this type. In the United States, England, and some other countries in which vaccination is not practiced as rigorously as could be wished, the disease nevertheless occurs in a very mild form nowadays, the so-called "varioloid," with a mortality rate not over 1 per cent. But the present mildness of the disease in these countries does not insure that the old malignant smallpox cannot easily establish itself again; indeed this happens now and then when smuggled labor from one of the endemic foci of classical smallpox is brought into a land in which the prevailing form is mild—for example, Mexican laborers have started several such outbreaks in the United States. The old malignant form of the disease also occasionally gets a start in a port city when a ship arrives from the Far East with an unrecognized case aboard; this happened in Glasgow in 1942 and caused a rapid spread of the disease and a number of deaths before the outbreak was tramped out by vaccination. The disease known in various parts of the world as alastrim, amaas, and parasmallpox is considered to be probably identical with mild smallpox, but students of the matter are still far from certain that it is so.

The black race is much more susceptible than the white. The disease is caused by an unidentified virus and is contagious by contact during any time that there are symptoms; it is probably also air-borne to some extent, at least such dissemination has not been disproved. It is more frequent during the colder months of the year. The average period of incubation is from ten to twelve days, but it may be from five to twenty-one days.

It is not in order here to describe the various types of smallpox, such as the confluent, the purpuric and the hemorrhagic; the following is a brief description of the classical type of attack. Onset is usually abrupt with a chill or chilliness, headache and severe backache, rapid and high rise in temperature and accompanying rise in pulse and respiratory rates, generalized body pains and nausea, and many times persistent and violent vomiting. Menstrual flow often appears out of its due order and abortion is frequent. About three days after the onset of the disease a macular eruption appears (on the face and wrists first) which soon becomes papular, and in another three days this has

become vesicular; some of the vesicles become umbilicated and multilocular. About the ninth day of the disease the pocks will have become pustular. Schamberg has estimated that in a case of moderate severity there may be as much as 5 quarts of pus contained in the pocks all over the body. At this stage the patient is often very odorous. Lesions, which stop short of vesiculation, are frequent on the mucous membrane of the mouth, nose and tongue; usually also there is enough involvement of the pharynx and larynx to make for extreme discomfort and hoarseness. At the appearance of the eruption the fever and other symptoms usually sharply subside, but this is not invariable; at this time also the patient may manifest signs of cerebral disturbance, which is usually more truly a dementia than a delirium. Following the afebrile period there is a second rise in temperature which coincides with the pustular stage of the eruption. This second period of fever terminates with the beginning of desiccation, about the twelfth day of the eruption, but may continue for a long time if the case has become one of secondary sepsis. One attack usually confers immunity for life but rare second and even third attacks are on record.

During War II, van Rooyen and Illingworth (1944) became convinced from their considerable experience with smallpox in the Middle East that early diagnosis is much facilitated by the employment of a laboratory test in which skin scrapings are searched for what are known as variola "elementary bodies." In 80 cases ranging in severity from mild to fatal hemorrhagic forms the laboratory and clinical findings corresponded in 77 instances (*i.e.*, 96 per cent). The elementary bodies were said to have been demonstrated with ease in the papular and vesicular stages but they tended to disappear after the onset of pustulation. In no instance in this series did a positive laboratory verdict disagree with the final clinical diagnosis of the case, but negative laboratory findings were returned in 3 cases which proved clinically to be smallpox. Van Rooyen and Illingworth found that the test was not applicable to the diagnosis of chickenpox.

THERAPY

Symptomatic Therapy.—In the initial febrile stage of the disease only symptomatic therapy is indicated. A nutritious diet and plenty of fluid should be provided as in all infectious diseases. In the beginning it is desirable to relieve the severe pains by the use of such remedies as acetylsalicylic acid, 10 grains (0.6 Gm.) every three or four hours, phenacetin, in the same dose and at the same intervals, or amidopyrine in a dose of 5 grains (0.3 Gm.) (see under Agranulocytosis for toxic action of this drug). Sometimes these milder agents will not suffice, and morphine or dilaudid must be given. The vomiting is perhaps best controlled by gastric lavage with 1 per cent sodium bicarbonate solution; it has been said that the slow intravenous injection of dextrose solution will sometimes stop it also.

The severe itching that often occurs is much relieved by the following lotion, which has the objection, however, that it dries into a thin crust that may aggravate the condition unless it is frequently washed off with olive oil, not with water.

℞	Phenol	ʒss	2.0
	Prepared calamine	ʒiiss	10.0
	Zinc oxide	ʒiiss	10.0
	Glycerin	♏xi	2.4
	Solution of calcium hydroxide to make	℥iv	120.0

Twenty per cent argyrol solution should be dropped into the eyes twice daily from the beginning, and one should be especially attentive to the possibility of scarring from conjunctival lesions if the face is so much swollen as to close the eyes. Haughton (1942) recommended instead of argyrol for the eyes that one wash them often with boric acid or saline solution, apply drops of 1:1000 acriflavine three times daily, and at bedtime without fail introduce half-strength yellow oxide of mercury ointment.

Wilkinson (1943) wrote in rather general terms of the promising results obtained with convalescent serum. The serum was obtained from patients who had had smallpox for at least thirty days; no evidence was cited as proof of his contention however. Illingworth and Oliver (1944) gave convalescent serum to 3 patients expected to have a severe attack and they all died.

Minimizing Scarring.—If scratching were the chief factor in scarring then it would seem that children should be the most afflicted in this regard; the fact is, however, that the cosmetic result is very much better in children than in adults. Scratching is of course to be resisted as much as possible for it certainly increases the liability of secondary infection. It has long been held that painting the individual lesions with diluted tincture of iodine or with 5 per cent potassium permanganate solution several times daily will promote healing and minimize scarring, but I have never seen a report of a real study of this procedure. In a small family outbreak, McCammon (1939) treated 4 of his patients with sulfanilamide and 3 without; the untreated patients all developed the typical eruption, but in 3 of the treated patients there was only an evanescent macular eruption which rapidly disappeared and in the remaining patient only three pustules developed. McCammon said that those who received sulfanilamide were back at work about a week sooner than those who did not. Patel and Naidu (1940), of India, and Wilkinson (1942), of Hong Kong, found that in the septic pustular stage the sulfonamides undoubtedly diminished fever and reduced complications and also effected a considerable reduction in the mortality rate. However, Illingworth and Oliver (1944) gave sulfonamides to most of their 100 patients and felt that these drugs influenced neither the course of the disease nor the extent of the scarring; indeed, they cultured the contents of unbroken pustules in 15 cases and since every culture was sterile they found it difficult to understand how sulfonamides could be expected to be of value in reducing scars. I have seen only one report of the use of penicillin, that of Jeans *et al.* (1944), who treated 4 patients with severe confluent smallpox with this new agent at the height of the eruption; 3 of the patients survived including one who had never been vaccinated. Haughton (1942), who wrote reminiscently of many years' experience of smallpox in India, stated that xylol taken internally causes a flattening of the eruption, prevents suppuration and reduces scarring to a minimum; he said it also greatly reduces mortality but that its employment *must* be begun very early in the disease. Haughton's xylol dosage for an adult man was 30 minims (2 cc.) four times a day in milk for three days, then thrice daily for three days, then twice daily for three days, and then stopped; the dose was reduced to 20 minims (1.2 cc.) for women, to 10 minims (0.6 cc.) for children and 5 minims (0.3 cc.) for infants. This agent has cropped up a number of times before in the earlier literature of smallpox and very probably has value.

Removal of Scars.—The use of trichloracetic acid was said many years ago to be sometimes successful in removing smallpox scars (Wise, 1920). Fisher (1938) reported the removal of an accidental (autovaccination) scar by the use of blistering doses of ultraviolet rays.

PROPHYLAXIS

It is said that the Chinese have for many centuries practiced a crude kind of vaccination by thrusting human smallpox scabs up the nose. The Turks had refined upon this somewhat in that they introduced some of the pus from such a scab into a small incised wound of the arm; after an incubation period of a week or so the patient experienced a mild attack of the disease and was then immune. This was the practice which Lady Montagu brought home to England in 1727, where, after some preliminary opposition, it was much used until supplanted by the Jenner method; it also had considerable vogue in the American Colonies—Krafka says that general inoculation of the army occurred during the Revolution. Schamberg says that the custom never enjoyed much popularity on the Continent. By all accounts these induced cases were by no means invariably mild. Jenner, in England, conferred upon the world the great boon of vaccination with the virus of cowpox in 1798.

In what follows, I have drawn upon authoritative sources to supply answers to the chief annoying questions which arise in connection with present-day vaccination.

Method.—In 1936, Sanford described the method very graphically and I cannot improve upon it: "The site of vaccination should be thoroughly washed with acetone. Other antiseptics may destroy the virus. A drop of virus is placed in the center of the cleansed area. Holding a small sterile needle at an angle of 20 degrees from the skin surface, the point of the needle is pressed into the skin through the drop about ten times. Obviously these pressure points should be in the same locality. No blood or serum should be drawn. The excess of virus is now wiped off with a piece of sterile gauze. There is some difference of opinion as to the advisability of putting a dressing over the inoculation. It is permissible to use no dressing. Certainly tight constricting bandages and shields should be strictly avoided. I always put one thickness of sterile gauze over the point of inoculation very loosely with a piece of tape. The mother is told to remove this next morning and put nothing more on it until the pustule appears. She is then told to place a similar piece of gauze on the pustule, and to change it daily unless the pustule breaks and sticks to the gauze. If this happens the gauze is not removed. No tub bath is given the child from the time the pustule appears until the scab is on firmly. The mother is warned that a papule usually appears on the third to fifth day. In another day this becomes a vesicle and the next day a pustule with a swollen red area about it. At about the sixth day there is frequently some fever and loss of appetite. Mothers are told to report one week after vaccination for inspection and further instructions." Leake (1943) emphasized the fact that proper refrigeration is of the utmost importance in the preservation of smallpox vaccine; he stated that the vaccine should be shipped by the manufacturers packed in dry ice and that it should be kept in the freezing compartment of the refrigerator. Trommer (1943) advised that when performing mass vaccinations in a clinic during an epidemic it is advisable to wear rubber gloves in order to avoid acquiring undesirable vaccinations on one's own person (as he did on both thumbs!).

Choice of Sites.—Boys, over insertion of deltoid muscle on left arm. Girls, outer aspect of left thigh, two thirds of the way from knee to hip. It is worth noting that leg vaccinations are more likely to cause large scars than arm vaccinations and that primary leg vaccination in adults may be accompanied by purplish discoloration and cause temporary disability.

What Is a Successful "Take"?—(1) Redness, passing in eight to seventy-two hours, accompanied by slight elevation of the skin and perhaps itching, indicates immunity at the time of vaccination. (2) A greater degree of this, lasting three to seven days, indicates that there was only partial immunity. (3) With the typical full take, indicating no immunity at the time, the red areola reaches its broadest diameter in eight to fourteen days after vaccination and there is a turbid, whitish vesicle, which may or may not become a pustule before it dries and promptly heals. All three of these reactions are "takes" because they indicate the degree of immunity and raise it again to maximum. Leake, of the U.S.P.H.S., said that all other results indicate deficient vaccine if the technic was proper and the individual in good health.

Complications.—(1) Excessive swelling, abscess formation and lymphatic enlargement indicate secondary infection. Cleanse the pustule with ether and paint with mercurochrome or gentian violet or metaphen solution. Abscesses to be treated surgically with wet dressings. (2) Generalized vaccinia; rare. Pustules around lesion or scattered papules and vesicles over body. Usually only slight fever and prostration. Prognosis excellent and recovery rapid. (3) Autovaccination, caused by failure to wipe off excess of vaccine and the child's finger carrying it to other parts of the body; or child scratches the uncovered pustule. New pustules will be similar to original and are cause for no concern unless involving eyelid or cornea—which calls for ophthalmologic consultation at once. (4) After about 500,000 vaccinations in the summer of 1942 at Glasgow, a report was made by Bloch (1942) of 123 regional or generalized postvaccinal rashes, the majority of which appeared seven to eleven days after well-marked positive primary vaccinations in children. A regional papular eczema erupted seven weeks after vaccination of an infant. Diagnostic difficulty was at first considerable but soon diminished except in some cases of papular urticaria. Of 98 erythematous or urticarial eruptions, 37 were papular urticaria and 20 pleomorphic types of erythema multiforme. A previously healthy breastfed boy positively vaccinated at a vaccination station when aged eight weeks died ten days later of exfoliative dermatitis on the sixth day of illness or fifth day of the complicating eruption; the complicating disease was regarded as staphylococcal. Davidson and Davis (1943), reporting on findings during the same period of mass vaccinating in Scotland, listed four patients ranging in age from four to forty years who developed abnormal reactions eight to ten days after vaccination. Purpuric manifestations appeared in 3 of the patients, 2 of whom developed well-marked edema at the same time; the remaining patient showed generalized vaccinia. It was believed that these abnormal reactions might have been related to an allergic tendency, but it does not seem to me that a very clear case was made out for this hypothesis. (5) The British statistical study of 1931 revealed that for each million persons vaccinated for the first time there are nineteen disorders of the nervous system, with six or seven deaths, and for each million persons revaccinated there is one such disorder, with a fatal issue. The report of Anderson and McKenzie (1942), following the vaccination of about 500,000 persons in Glasgow, very well confirmed the above findings since there occurred in this group 7 cases of postvaccinal encephalomyelitis of which 2 died; 6 of the 7 cases were in persons over five years of age vaccinated for the first time. Clearly, there is no cause for anxiety here. Since the great majority of the cases are in children primarily vaccinated between the ages of three and thirteen, the well-established precept of vaccinating in early infancy is roundly confirmed. Jorge's (1932) study

of these postvaccinal nervous disorders was most exhaustive. It is probable that little if any risk attaches to the revaccination of a person who has suffered postvaccinal encephalitis years before.

How Long to Continue Trying If No "Take" Is Obtained?—Failure to obtain one of the three kinds of reaction described above under "successful 'take,'" does not indicate immunity but only unsuccessful vaccination. Repeat at two-week intervals until a "take" is had—there is a record of thirteen attempts before success was attained. It is likely that many failures to obtain a "take" are due to ignorance of the facts regarding storage of the vaccine which I have already mentioned under "Method."

Best Time of Year.—Hot months predispose to infection because of perspiration and scratching; in winter and early spring there are the respiratory infections which unintelligent parents may charge against the vaccination. This leaves late spring and fall as the ideal seasons—but this matter is not of much importance.

Contraindications.—Women may be vaccinated at any time during pregnancy without fear of obstetrical complications, but successful vaccination of the mother does not convey specific immunity to the infant. It is best not to vaccinate during menstruation. Eczema, impetigo, furunculosis or other "open" skin diseases or fissures, ulcers, burns, or wounds should cause postponement unless there is an epidemic; likewise gastro-intestinal upsets or malnutrition. Acute infectious diseases may cause delayed or atypical "take" but are not in themselves contraindications in case of possible exposure; however, Stitt (1943) cited the case of a child whose symptoms of postinfectious encephalomyelitis following measles were just beginning to subside when he was vaccinated for smallpox and in whom there occurred a marked increase in encephalomyelitic signs and symptoms following the vaccination. Lymphomatous diseases, such as leukemia and Hodgkin's disease, may be made worse.

In adult pulmonary tuberculosis vaccination apparently may be performed with little risk if exposure necessitates, but in tuberculous children, and in bone tuberculosis at any age, one should be very cautious as some unfortunate results have been reported (J.A.M.A., 102: 233, 1934). The diabetic, with his easy infection by pyogenic bacteria, should perhaps be vaccinated only during an epidemic. Vaccination is not contraindicated in asthmatics or other allergics but such individuals may have more pronounced reactions, both local and constitutional. An asthmatic attack may be precipitated, but what is more likely is that during the vaccination reaction the allergic symptoms may recede as they often do in the presence of intercurrent disturbances.

Lapse of Time from Vaccination to Protection.—Successful vaccination performed on the day of exposure will almost always completely protect; performed up to a few days before onset of the disease it will at least make the attack milder.

It is roughly true that the individual is protected completely twelve days after performance of vaccination; but since the vaccination may not "take" the first time it is tried, it may be wise to vaccinate twice if an individual presents himself within four days of the time of known exposure, the second time two days after the first and 2 inches removed from it.

Duration of Immunity.—It is estimated that protection in white persons lasts from seven to ten years and in the Negro four years; but this is largely a gratuitous assumption using the magical numbers seven and ten. As a matter

of fact, not many reliable data are to hand for the reason that all three types of "take" (see above) must be carefully observed and recorded if the statistics are to have value. Until very recently failure to obtain any sort of reaction was often interpreted as evidence of retained immunity, whereas we know that this only indicates unsuccessful vaccination. The authoritative study of Dearing and Rosenau (1934), on medical students at Harvard, indicated that the immunity conferred by a single vaccination lasts twenty years or more in most individuals; welcome news, but since 1 of the 22 students revaccinated less than five years after the first successful vaccination gave a primary "take" (evidence of complete loss of immunity), we are not helped much in determining the absolute minimum duration of protection. However, it may be that infection with smallpox is more difficult after successful vaccination with cowpox than is reinfection with cowpox on revaccination. Coleman (1944) cited the case of a man walking about freely among his companions in the close conditions of barrack life for eighteen hours during the prodromal stage of virulent smallpox without the development of a single other case, though upon immediate revaccination of the entire unit of 938 men upon the diagnosis of this case, 5 per cent of them developed "takes" though all of them had been previously vaccinated within a five-year period.

When and How Often to Vaccinate.—In view of what has just been said above, it is apparent that we have no absolute guide. The following seems to be reasonable: Children should be vaccinated before six months of age, again on entering school, and again at puberty; all children and all adults should be revaccinated when there has been a known exposure, when an epidemic threatens, or upon visiting a region where foci of the old malignant form of smallpox are known to exist. If the newborn infant is mature at birth vaccination at this time is a safe procedure with negligible complications, insignificant influence on growth and nutrition and a very high percentage of "takes" almost always without fever (Donnally *et al.*, 1934–1940); but, as Doull (1934) pointed out, the first day and week being the time of greatest mortality from other causes, some of these deaths may be erroneously attributed to vaccination.

In our Army during World War II, according to Minning (1944), revaccination was performed at three-year intervals, in addition before departure for overseas duty unless the individual had been vaccinated within the twelve-month period prior to departure, and also upon exposure to smallpox or in the presence of an outbreak regardless of date or result of the last vaccination.

Effect of Vaccination on Serological Test for Syphilis.—Lynch *et al.* (1941) observed false positive reactions for syphilis in 16 per cent of 263 persons studied after primary vaccination and said that such false positive reactions may persist for several months; the incidence in Favorite's (1943) series of 202 patients was 11.8 per cent, and he found a gradual diminution in the intensity of the reactions until all had become negative by the end of 120 days.

Immunization Schedule.—Peterman's (1942) observation and immunization schedule for infants from birth to one year is included here as a very practical guide for conduct of the first year of life, though I am aware that there are differences of opinion among pediatricians with regard to the exact time and chronological order of the various immunizations.

At birth look for:

1. Prematurity—weight under five pounds
2. Areas of atelectasis—treat with oxygen
3. Imperforate anus—have surgeon operate
4. Congenital heart disease
5. Hydrocephalus
6. Wryneck—correct early
7. Clubfoot—correct early
8. Dislocated hip with gluteal folds absent or shallow and trochanters not symmetrical—correct early
9. Jaundice

One month:

1. Start cod liver oil and orange juice
2. Look for Erb's palsy and umbilical hernia—strap with waterproof adhesive after folding in umbilicus

Two months:

1. Weight and measurement—monthly
2. Ability to hold up head
3. Check formula

Three months:

1. Prevent thumb and finger sucking

Four months:

1. Child's birth weight should be doubled
2. Add cereals to diet
3. Look for rickets and anemia; will be found in half of the infants
4. *Smallpox* vaccination

Five months:

1. Addition of more cereals to diet
2. Postural ability
3. Posterior fontanel closed

Six months:

1. Postural ability (baby should sit up alone)
2. Add vegetables to diet—properly canned are preferable
3. *Whooping cough* immunization

Seven months:

1. Add egg yolk to diet except in eczema

Eight months:

1. Add scraped beef and baked potato to diet
2. Whole milk diet (no sugar)

Nine months:

1. *Diphtheria and tetanus toxoids* combined—first injection
2. Add zwieback and mashed fruit and gelatin

Ten months:

1. Should stand alone

Twelve months:

1. Three meals a day
2. Final monthly examination
3. Baby starts to walk and talk
4. Examine urine
5. *Diphtheria and tetanus toxoids* combined—second injection (six weeks later Schick test and repeat every five years; repeat tetanus toxoid every two years)
6. Complete physical report given to parents

SYPHILIS

Syphilis is a venereal and general constitutional disease, caused by *Treponema pallidum*. Whether or not it was unknown in the civilized world prior to the first return of Columbus from Haiti, in 1493, is a controversial point about which discussion is so warmly waxing in recent years that I now humbly hesitate to commit myself so fully as I did in earlier times. However, there is agreement on the following two points at least: That at the end of the fifteenth century syphilis was spreading widely throughout Europe (or the physicians of the Renaissance were suddenly awakening to its presence), and that recognition of the entity and realization of its importance have been steadily increasing since that period. The trend of the incidence of syphilis seems to be upward in many civilized countries today, though it is definitely declining in others, particularly in small countries with homogeneous, highly literate and easily accessible populations. Under the impact of the great attack upon the disease launched by Surgeon General Parran a few years ago a rapid decline in incidence might have been expected in the United States, but of course War

II disturbed the normal course of events. When full mobilization began, syphilis rates in the Army increased slightly, then levelled off and finally declined to a new all-time low; the case rate in the Navy declined remarkably also. I believe there are no data available on a national level to show what has happened to the syphilis rates among the whole civilian population during this time, but according to Heller (1944), Assistant Surgeon General, U.S.P.H.S., preliminary analysis of the data obtained upon registration of 14,000,000 men for selective service indicated that approximately 710,000 of them had evidences of syphilis. This would indicate that the war has so far not brought an increase in the amount of syphilis in the nation, which is an astonishing thing since all previous wars have been characterized by such an increase. Undoubtedly the great reservoir of syphilis in America is the Negro, not because he is the Negro but because he is a member of a race discriminated against economically and socially. Incidence has usually been found to be high in such primitive races as have been investigated from this standpoint; for example, a 50 per cent infection rate based upon clinical observations only has been determined in certain nomadic tribes of eastern Siberia. Of very great interest are the observations of Hudson, who alleges that there is a Bedouin population in the valley of the middle Euphrates River in whom the disease, there known as *bejel*, exists as a completely nonvenereal contagious disease of children. There are those, however, who are doubtful of this nonvenereal characteristic, and Hasselmann, who undertook an investigation for the United States Public Health Service, flatly denies it. Some men look upon bejel and yaws as the same thing and others consider that bejel may be a disease intermediate between yaws and syphilis. The earlier belief that classical neurosyphilis does not occur among primitive peoples in whom primary syphilis is untreated is now entirely discredited; that its rarity in certain regions despite a high incidence of syphilitic infection *per se* may be due to the endemicity of malaria has been interestingly discussed, *pro* by Needles (1935), *con* by Franke (1933). Studies performed in several of our neighboring Latin American countries to the south seem to have gone far toward establishing pinta, a nonvenereal type of spirochetosis whose distribution is limited almost exclusively to the dark races, as identical with syphilis; Lieberthal (1943) described the first three cases of this malady in the continental United States.

Syphilis is usually acquired by sexual intercourse with an infected person, but the incidence of innocent transmission is higher than is generally believed. In Clarke's (1939) analysis of 971 cases of syphilis diagnosed in the chancre stage in clinics of the New York Department of Health, 5.7 per cent were found to be extragenital. The seriousness of early unsuspected syphilis of this type is evidenced in such reports as that of Rowntree and Hendon (1940) who found extragenital transmission of the disease among five persons in one family. Ingraham and Hesse (1944) reported the transmission of syphilis from a mother to her child *in utero*, and from the child, after birth, to the father by contamination of his conjunctiva.

In the classical case of syphilis, venereally acquired, the course is generally the following: (*a*) The appearance of the primary sore (chancre), which is multiple in about 25 per cent of the cases, after an average incubation period of twelve to forty days. (*b*) The appearance of secondary symptoms at an average time of eight weeks after the appearance of the chancre: skin rashes of such varied sorts as to make description impossible here; mucous patches in the mouth or anal region, plus the symptoms which often accompany gen-

eral infections in greater or less degree, such as malaise, fever, anorexia, sore throat, headache and joint pains and nervous manifestations; very rarely acute nephrosis. (*c*) A so-called "latent period" during which the infection is apparently quiescent for a variable term of years. (*d*) The appearance of the "tertiary" period of the disease, which is characterized by protean and serious symptoms which are due to gummatous, or more diffuse, pathologic disturbances which may occur in any portion of the body.

The above classification into primary, secondary, latent and tertiary stages is largely arbitrary and is by no means clearly demarcated in all cases. The symptoms in congenital syphilis are in the main the same as those in the acquired variety except that the primary sore is lacking and that the type of damage peculiar to the tertiary period is usually caused early in the life of the patient. The fetus is infected *in utero* by the mother, who must herself be first infected.

INTRODUCTION TO CURRENT METHODS OF THERAPY

In 1928 the League of Nations Health Organization initiated a world-wide survey of methods and results obtained in the treatment of syphilis. The study was carried through in the United States by the Cooperative Clinical Group, comprising the syphilis clinics of the Universities of Pennsylvania and Michigan, Western Reserve University, Johns Hopkins University, the Mayo Clinic and the United States Public Health Service, the findings being published in the period 1934–1938. In these findings there were definitely established certain facts, to wit: (*a*) It was shown that if the patient is not treated in the beginning of the infection, serious late syphilis may be expected in about 25 per cent of instances, benign late syphilis in 15 per cent, latent syphilis in 30 per cent and spontaneous "cure" in 30 per cent. But if the patient is treated early, continuously and adequately, complete cure may be expected in nearly 90 per cent of instances, with symptomatic cure but retention of a positive blood Wassermann in another 5 per cent. Therefore, in reply to the patient's question "What are my chances of becoming and remaining well with no further trouble from this disease?" the Cooperative Group provided the reply "About 90 per cent if you are properly treated and if you cooperate fully and bear the drugs well." (*b*) It was shown that the prospective cure drops about 20 per cent if treatment is not begun until the blood tests become positive or the secondary manifestations appear, but it should be remarked that this is "cure" in the purest sense of the word, *i.e.*, both symptomatic *and* serologic cure; symptomatic cure alone can apparently be accomplished as well if treatment is begun in the early secondary stage as in the primary stage. It is an interesting observation that the mucocutaneous type of relapse occurs less often in the patient whose treatment was not begun until after his secondary manifestations had developed, but this does not by any means point to the advisability of delaying treatment until the secondary stage is established since the likelihood of cure is so much greater if treatment is begun earlier even though the patient is admittedly slightly more likely to experience mucocutaneous recurrence, and therefore a somewhat prolonged period of infectiousness, if he is not allowed to enter the secondary stage before beginning treatment. (*c*) It was established that if treatment is begun at once when the disease is in the seronegative primary stage, and that if it comprises overlapping courses of arsenic and bismuth, the patient may be cured in twelve months if he is treated continuously without any rest periods during that time

and receives 30 intravenous injections of an arsenical and about the same number of intramuscular injections of bismuth, the course of the bismuth injections to overlap always the end of the arsenical courses. The patient whose treatment did not begin until he was in the seropositive primary or early secondary stage must be treated for eighteen months, during which he will have received half again as much of both arsenic and bismuth, and his cure is not quite so certain of being achieved. (*d*) The findings of Padget (1941), of the Johns Hopkins group, whose 551 patients were clinically and serologically negative five years after treatment and were still negative after another period of five years had elapsed, were held to justify the conclusion that in early syphilis five-year cure means permanent cure.

Now the tying together of all the above observations and facts served to establish the "standard" type of treatment which was pursued with great success in this country for a number of years, for the reason that it could assure to the completely cooperative patient a cure within a year to a year and a half in about 90 per cent of instances. And it had the further great advantage of being able to offer the patient this high prospect of cure coupled with the assurance that the treatment regime he was to follow would hardly at all endanger his life. However, if success was to be attained with this method there was required of the patient an amount of cooperation and expenditure of time which even the foremost champions of the method admitted he was willing to supply in no more than half of the instances in clinic practice. Therefore there have arisen foreshortened "intensive" methods of treatment, which were rationalized by Eagle and Hogan (1943), who showed in both animal and human studies that syphilis can be cured in 80 to 100 per cent of cases, depending upon the stage of the infection at the time treatment is begun, by a total dose of 20 to 30 mg. per kilogram body weight of mapharsen alone. It was further established that the toxicity of this dose of arsenical is inversely proportional to the time in which it is given; *i.e.*, within the limits of therapeutic efficacy, the greater the span of time through which the treatment is extended the smaller the chance of killing the patient. Therefore in a given case of early syphilis one can choose to effect a cure in a few days or weeks or months or a year or so, basing his choice entirely upon the risk to life he believes to be justified in the individual instance. Thus the mortality risk of the five-day intravenous drip method, which may be taken to be the most intensive of the methods currently employed, is authoritatively estimated at 1 to 200 to 1 to 300, while that of the "standard" method developed through the studies of the Cooperative Group and described above, and now looked upon as the most conservative type of treatment, may probably be placed at about 1 to 4000 if one thinks of its employment in terms of mapharsen, which is the drug universally employed nowadays in the quicker methods. Therefore, if one says that in a given case the degree of emergency which exists should alone guide the choice of a type of treatment and hence the choice of mortality risk, the whole truth will have been stated, except for one very important fact—namely, that in the more conservative types of treatment full success can be attained only if the patient is completely cooperative throughout, whereas in the intensive types of treatment, particularly the most intensive types which require hospitalization, the patient is obliged to take all of the treatment because he is under full control during the whole of the time. I have the feeling that the most intensive types of treatment are destined to attain an even greater popularity than has been achieved by them so far for

the reason that, despite their high mortality, they do force cooperation and hence cure in the type of clinic patient who is most prone to discontinue treatment very early in one of the more conservative methods. It seems to me that the fate of the most intensive types of treatment in private practice is still anybody's guess. And of course what place penicillin will ultimately take in the picture is as yet undetermined.

In recent years there have been set up in this country a number of types of "intensive" treatment, the study of all of which of course has been much stimulated by War II. Even had I the time and the space I could not describe all of these methods here nor would I be justified in doing so because many of them are still almost completely experimental. However, I think the general practitioner will want to know just how to treat a patient by (*a*) the most intensive of the methods, in which he hospitalizes him and has the whole thing over in a few days; (*b*) by the Army method, in which six months (twenty-six weeks) is allowed for the treatment, which is of course of the ambulatory type; and (*c*) by the standard, now known as the "conservative," method of the Cooperative Clinical Group, in which the patient is treated for a year to a year and a half. These three types of treatment of early syphilis will therefore be described together with such records of accomplishment with penicillin as have already appeared in the literature.

The Penicillin Treatment of Early Syphilis

In September, 1944, the Penicillin Panel of the Subcommittee on Venereal Diseases of the National Research Council reported, in a paper appearing in the bibliography of this book as Moore, Mahoney *et al.* (1944), on the treatment of 1418 cases of early syphilis with penicillin. This was a composite report of the results obtained in a large number of clinics in which the agent is under expert and careful study. The findings may be briefly listed as follows: (*a*) With a total dosage of 60,000 units in eight days, healing is less prompt than with arsenical therapy; with larger dosage, 300,000 units and up, it is as rapid as with standard chemotherapy or perhaps even more so. (*b*) Regardless of the single or total dose of penicillin, organisms promptly disappeared from open lesions in every case within a range of six to sixty hours. (*c*) Regardless of the total dosage, whether 60,000, 300,000, 600,000, or 1,200,000 units, there was a trend toward serologic reversal within a period of about twenty days after the start of treatment; within the range of 300,000 to 1,200,000 units this trend was approximately uniform regardless of the dosage, but with 60,000 units it was a little slower and less pronounced. Otherwise stated, the rate of serologic reversal was identical with that observed under any of the types of arsenical therapy. (*d*) The relapse rate for patients with seronegative primary syphilis was 3.2 per cent during the period of observation, and using incidence of relapse as a criterion of effectiveness of therapy it was not possible to make a statement as to minimum effective dosage at the time of the report. But in seropositive primary and early secondary cases it was shown that any dose less than 600,000 units in seven and one-half days was clearly ineffective since this dose provided a minimum relapse rate of nearly 5 per cent, whereas 1,200,000 units gave a relapse rate of only 2 per cent. It was felt, however, that perhaps even 1,200,000 units in a four- to eight-day period would prove inefficacious after further observation, and therefore studies employing 2,400,000 units in 30 and 60 intramuscular injections (four and seven and one-half days respectively) were instituted, but at the time of the present writing they have

not yet been reported upon. (*e*) The intravenous route of administration appeared to be less effective even in large doses than the intramuscular. (*f*) Herxheimer reactions occurred in 59 per cent of the 1418 patients. They consisted usually of fever alone but in some there was exacerbation of skin lesions with or without fever. The symptoms were usually mild and the reactions did not interfere with subsequent treatment. In no case was it necessary to suspend penicillin treatment because of any other type of reaction. (*g*) Until methods are developed which will permit the employment of penicillin on an ambulatory basis it is certainly not suitable as yet for mass application, the reason being that the necessity for giving injections every three hours day and night demands hospitalization and trained nursing and professional care to an extent not ordinarily available, even in peacetime, in civilian practice.

The Five-day Chemotherapy of Early Syphilis

This is the type of treatment which has gained great impetus since about 1940 under the leadership of Hyman, Chargin and Leifer. It is to be understood that both the five- and ten-day types of therapy for early syphilis are designed for employment only in robust young people, especially men, who are reasonably free from serious visceral disease such as hepatitis, myocarditis, severe hypertension, nephritis, excessive alcoholism, blood dyscrasias, active pulmonary tuberculosis, and who have received little or no previous antisyphilitic therapy and have no history of serious arsenical reactions. Also before treatment is instituted the patient is to undergo a complete physical examination and there are to be determined the urea nitrogen content of the blood, the icterus index, a complete blood count including that of platelets, full serological examinations preferably made by several laboratories, dark-field examination of material from all open sores, and estimations of renal and hepatic function. It is not considered advisable to administer sulfonamides while these intensive types of therapy are under way.

Procedure.—The patient is to be in bed and is to have a high calorie diet, rich in starches and carbohydrates; many patients gain several pounds during the few days of treatment. An enema is routinely given the night before treatment is to be begun and thereafter the attempt is made to evacuate the patient's bowel by the use of an enema each evening to obviate the necessity for employment of the bedpan while the treatment is under way during the day; the patient can of course handle a urinal since he has one arm and hand free and can feed himself from an ordinary bed tray. The treatment is begun early in the morning with the insertion of a 20 gauge 1½-inch needle up to its hub in a vein on the forearm between the elbow and wrist in order to allow movement at both of these joints, the needle being held in place with adhesive or scotch tape and alternate arms being used on succeeding days. The tube containing the mapharsen solution is then attached to the needle and after 10 or 15 cc. have entered rather rapidly the flow is regulated to about 50 or 60 drops per minute so that from eight to twelve hours is required for the introduction of the full 2000 cc. of fluid. After the therapy has been discontinued in the evening the patient may get out of bed.

Dosage of Mapharsen.—The total dosage for patients weighing less than 70 kilograms (155 pounds) is 1000 mg. (1 Gm.); for those weighing 70 kilograms or more it is 1200 mg. (1.2 Gm.). The amount administered each day is one fifth of the total, but if on any day the amount received is less than the daily allotment the surplus from that day must be spread out equally through

the remaining days. The mapharsen is dissolved at the rate of 10 mg. per 100 cc. of 5 per cent dextrose solution, often 500 cc. of such solution, which is about enough for three hours, being prepared at one time; frequently, however, a Vacoliter containing 2000 cc. of 5 per cent dextrose is used and the total amount of 0.24 Gm. of mapharsen is added in the morning for the whole day's run.

Dosage of Bismuth.—It took the exponents of the intensive types of treatment quite a while to get around to a realization of the value of the concomitant administration of bismuth, but now they have done so and such practice is practically universal. The advantage of using bismuth was shown in such studies as that of Rattner (1943), who felt that in his 421 cases the satisfactory results from one course of treatment in 86 per cent treated with arsenic alone were increased to 95 per cent when bismuth was used in addition. The method of using the bismuth is not yet standardized, some men giving an intramuscular injection of the usual size every day, as did Rattner, while other men inject only every other day.

Follow-up and Retreatment.—It is the consensus that the patient should have complete physical and quantitative blood serologic tests at monthly intervals for six months, the latter being repeated at the ninth and the twelfth months. According to Stokes *et al.* (1943) the blood serologic reactions usually become negative at the twelfth to sixteenth week after the start of treatment. Examination of the spinal fluid should be done some time between the sixth and the twelfth month. It is considered that a patient who has become clinically and serologically "cured," and who has remained so until the twelfth month of observation, and in whom the spinal fluid is negative at that time, may be discharged as having responded "satisfactorily" to the treatment. Such a patient returning later with a new darkfield positive lesion is considered a new infection and may be retreated in the original manner. Patients who have been "unsatisfactorily" treated, *i.e.*, those who have experienced an infectious or a serologic relapse or who have remained Wassermann-fast for a six months period after treatment, may be retreated by intensive therapy unless they had a severe reaction during the original treatment. Rattner (1943) retreated 23 such patients and in none of them was there an allergic reaction or any other complication due to the second course of treatment: 8 of this group attained seronegativity; 9 showed satisfactory serologic improvement; 3 were still pending at the time of the report although the serologic titer was showing a progressive fall; and 1 case was lost from observation.

The Ten-day Chemotherapy of Early Syphilis

This type of treatment, which is usually known as the "multiple syringe" technic, differs from the five-day type of therapy in that the patient is not confined to bed during the day, and that instead of receiving the continuous intravenous infusion of the mapharsen solution during eight to twelve hours daily he receives only 2 daily intravenous injections from a syringe at approximately twelve-hour intervals.

Dosage of Mapharsen.—Patients weighing up to 70 kilograms (155 pounds) receive 50 mg. of mapharsen twice daily during a ten-day course; those weighing over 70 kilograms receive 60 mg. twice daily. Each dose of the drug is dissolved in 8 to 10 cc. of distilled water, aerated and rapidly injected intravenously promptly after preparation.

Dosage of Bismuth.—A bismuth injection is given intramuscularly on the

first, fourth, eighth and twelfth days during the course of this treatment, the patient having been held in the hospital for two days after discontinuation of the treatment for a check-up observation.

The Addition of Fever Therapy.—For several years Thomas and his associates, at Bellevue Hospital, have been studying the possibility of lowering mapharsen dosage through the concomitant employment of fever therapy; in the most recent statement of their technic which I have seen, that in the report of Thomas and Wexler late in 1944, it was stated that mapharsen was given in a daily dosage of 1 mg. per kilogram throughout the ten days, the average patient receiving 60 mg. daily; a large injection of bismuth salicylate in oil is given intramuscularly on the first, third, seventh and tenth days; and fever is induced by the intravenous injection of typhoid vaccine as follows: 0.1 cc. on the second day, 0.2 cc. on the fourth day, 0.4 cc. on the sixth day and 0.6 cc. on the eighth day. Thomas and Wexler acknowledged the therapeutic superiority of fever induction with the hypotherm cabinet but felt that its employment is less practical because of the necessary equipment and personnel required. These observers, who were able to review 2144 courses of rapid treatment for early syphilis, felt that their results were just as good when this type of fever therapy with reduced mapharsen dosage was employed as when higher amounts of mapharsen were used without fever; their death rate was certainly very much lower.

It is of interest that in an evaluation of all of the types of intensive arsenic therapy for syphilis, published by the United States Public Health Service in late 1944, it was stated that in an analysis of 4351 cases it was found that the best results followed the use of this multiple syringe technic combined with typhoid vaccine.

Reactions with the Intensive Types of Chemotherapy

The reader will find additional discussion of arsenical and bismuth reactions where the standard ("conservative") type of therapy is presented in detail.

Fever.—With the five-day intravenous drip, fever sometimes occurs on the first day but the temperature is usually normal by evening and fever does not recur the next day. The drip is not discontinued unless the temperature goes above 101.4° F. (38.5° C.), and if this becomes necessary it may be resumed on the next day. The Herxheimer reaction (a flare-up of the syphilitic lesions) usually accompanies this primary type of fever. If there occur secondary rises of temperature in excess of 101° F. (38.3° C.) at any time after the first day of treatment it is considered that the treatment should be interrupted because such secondary fever sometimes heralds the appearance of a toxicoderma; fortunately in the five-day intravenous treatment the fever usually occurs on the last evening of therapy.

Nausea and Vomiting.—Gastro-intestinal disturbance of this sort occasionally requires temporary discontinuance of treatment but is usually successfully combated by sedation and the administration of fluids by mouth.

Skin Reactions.—The "ninth day erythema" type of skin reaction, which consists of a morbilliform, scarlatiniform, or urticarial eruption without exfoliation, is not seen until after conclusion of the five-day intravenous drip therapy and usually clears up in a few days without treatment. When this reaction occurs during the ten-day multiple injection type of treatment it is looked upon as an indication for interrupting treatment since it is sometimes, though rarely, associated with toxic encephalopathy. True exfoliative dermatitis,

which of course requires permanent discontinuance of all arsenical therapy, has occurred extremely rarely in these intensive types of treatment.

Nitritoid and Precordial Reactions.—The nitritoid reaction practically does not occur when mapharsen is employed, but Falk and Rattner (1942) reported a type of very distressing precordial oppression which is occasionally seen during the five-day treatment.

Peripheral Neuritis.—Since mapharsen replaced neoarsphenamine in these intensive types of therapy peripheral neuritis is rarely encountered, and then only in the period succeeding the conclusion of the therapy. The symptoms usually consist in paresthesias without any objective findings and they disappear spontaneously though somewhat slowly.

Jaundice.—This complication has been very rarely encountered but when it does occur of course it calls for discontinuance of treatment, the pushing of a high-carbohydrate-low-fat diet, the injection of liver extract and the administration of 10 per cent dextrose solution intravenously.

Purpura.—Blood dyscrasias, of which purpura is the most common, have not often been encountered but when they occur treatment should be permanently discontinued. Schwind's (1943) study of the bone marrow of 14 patients under five-day intravenous drip therapy observed no effects on the bone marrow in these patients, so it would seem that the purpuric reaction is an evidence of individual idiosyncrasy to the arsenical drugs.

Renal Injury.—Occasionally there are traces of albumin and a few red and white cells appear in the urine, but severe damage to the kidneys has been rarely recorded. To be sure, Thomas *et al.* (1943) reported a case of acute nephrosis which occurred when they were administering mapharsen in large dosage on two days accompanied by artificially induced fever, but they did not report renal damage as occurring in their ten-day multiple injection with fever type of therapy. However, Rattner and Falk (1942) reported a patient on the five-day treatment who developed not only acute glomerulonephritis, anuria and uremia, but also hepatitis, ileus and pericarditis—and he recovered!

Encephalopathy.—Mild headaches which respond to aspirin or codeine seem to occur rather frequently under this type of treatment and are of no moment, but if the headache is severe and persistent and increases in intensity it must be looked upon as a probable prodrome of the toxic encephalopathy which is the most feared reaction in the intensive types of treatment. The other symptoms are vertigo, tremor, disorientation, apathy, mental confusion, occasionally nausea and vomiting, convulsive seizures, prolonged chorea and in some instances hyperthermia and death. The treatment of this reaction, according to Stokes *et al.* (1943), consists in: (*a*) repeated drainage of spinal fluid, withdrawing 20 to 40 cc. daily; (*b*) dehydration by use of intravenous 50 per cent sucrose solution, 50 to 200 cc.; (*c*) sedation as indicated; (*d*) epinephrine. Oxygen inhalations may also be given, but sodium thiosulfate has been shown to be of no value. Kalz and Steeves (1944) studied the prothrombin concentration of the blood in 15 patients under five-day treatment and found a marked reduction below normal in all of them; it is noteworthy that in their series the only instance in which the prothrombin reduction progressed significantly after termination of treatment was in a patient who died as a result of the treatment, but it does not follow that vitamin K administration (menadione) is indicated during the employment of these massive types of arsenotherapy because the prothrombin deficiency in these cases

probably evidences liver damage, which is the type of condition in which vitamin K therapy has not been shown to be of much value.

The Army (Twenty-six-week) Chemotherapy of Early Syphilis

During War II the Army did not adopt any of the rapid intensive types of treatment with arsenic and bismuth because of their high mortality rates, but the effort was made to effect a compromise between the conservative year to year-and-a-half type of treatment and these quicker methods. The result was a treatment scheme which employs mapharsen and bismuth, 60 mg. of the former and 0.2 Gm. of the latter in the form of bismuth subsalicylate in oil

Table 6.—Army Treatment Scheme

	Week	
Arsenoxide (mapharsen) intravenously twice weekly, total 20 injections	1, 2, 3, 4, 5	Bismuth subsalicylate intramuscularly once weekly, 5 doses
	6, 7, 8, 9, 10	Omit bismuth for 5 weeks
Omit arsenoxide (mapharsen) for 6 weeks	11, 12, 13, 14, 15, 16	Bismuth subsalicylate intramuscularly once weekly, 6 doses
Arsenoxide (mapharsen) as in first course, twice weekly, total 20 injections	17, 18, 19, 20, 21	Omit bismuth for 5 weeks
	22, 23, 24, 25, 26	Bismuth subsalicylate intramuscularly once weekly, 5 doses

as shown in the treatment scheme in Table 6 as published by Turner and Sternberg (1944). Individuals with primary or secondary syphilis are hospitalized for a few days until open lesions have healed and then the treatment is carried on as an ambulatory one. A serologic test is done at the beginning and the end of the scheduled course but treatment is discontinued according to schedule whether the reaction is positive or negative. After the completion of treatment the test is repeated at three and six months; if the reaction is negative after six months the case is classified as "results satisfactory," but if it is positive it is considered that further treatment must be given. It is thought advisable also that a spinal fluid examination be done as soon after the termination of the course of treatment as possible.

No accurate data on the results obtained by the employment of this system of treatment are yet available, but it is expected that it will accomplish as good results as any of the other systems since it employs the same amount of the active chemotherapeutic agents. However, Turner and Sternberg reported that the short-term results have been excellent and that from the standpoint of toxic reactions and practicability of administration this new Army scheme appeared to be definitely superior to the more conservative twelve- to eighteen-month plan of the Cooperative Clinical Group.

The Conservative (Cooperative Clinical Group) Chemotherapy of Early Syphilis

This is the type of therapy that had come to be the standard treatment employed in early syphilis in the United States before the advent of the new intensive types of therapy. I should like to repeat here that as good results can be accomplished with this as with the more rapid methods of treatment with these two differences only, first, that it takes a much longer period of time

Table 7.—30–60–03 Treatment Scheme

30 neoarsphenamine or mapharsen injections, 60 weeks of bismuth injections.
NO rest intervals in the arsenical phase, 3 years of treatment-observation.
0 = neoarsphenamine or mapharsen; x = bismuth subsalicylate; weekly intervals.

```
 A  1          B  2     C        3        4        D
 ↓             |  ↓     |        ↓        ↓        |
00000000   0000↓ 0000  ↓00000000  000000          ↓
      xxxxxx        xxxxxx        xxxxxx     xxxxxxxxxx  8 weeks rest
5
↓
xxxxxxxxxx  8 weeks rest (and continue this intermittently to a total of 60 bismuth
  injections).
```

A = first 3 injections compressible into 10 to 14 days. Some risk of increased reactivity.
B = average case seronegative, 16th week.
C = Examine spinal fluid if blood is still positive, 24th week.
D = Always insist on spinal fluid examination before rest period.
1 = if blood test has become negative, suspect low resistance.
2, 3, 4, 5 = if weak positives appear among negatives, suspect relapse, neurosyphilis.

to cure a patient in this conservative fashion, and second, half or more of the patients tire of the treatment and give it up long before it has been completed. This system, to be presented here in the slightly modified form in which it has been recently employed, is sometimes known as the 30–60–03 method of treatment, the "30" representing the number of arsenical injections; the "60" representing the number of injections of bismuth subsalicylate at the rate of one a week; and the "0" and the "3" representing respectively no rest periods and three years of combined treatment-observation, the latter term meaning the total elapsed time from the institution of treatment until the patient is discharged from observation as presumptively cured. The treatment scheme as diagrammed by Stokes *et al.* (1943) is presented here in Table 7. The reader should bear in mind however that the 30–60–03 schedule shown in this table is that which the Cooperative Clinical Group found most effective for the treatment of seronegative primary syphilis and fully developed secondary syphilis. In a case of seropositive primary syphilis, or in a case of initially negative primary syphilis in which a positive blood test can be obtained on the day following the first arsenical injection, there was found to be a considerably greater likelihood of relapse than in seronegative primary or early

secondary cases. For such cases therefore it is proposed that a 40–80–04 system be employed, meaning thereby an additional 10 arsenical injections and 20 bismuth injections and another year of observation over and above the standards proposed as generally applicable to early and early latent syphilis. Such extension of the treatment scheme can take the form of 5 courses of the arsenical of 8 injections each in place of the 3 courses of 8 and 1 course of 6 injections in the 30–60–03 system; the bismuth therapy may follow the usual 2-injection overlap plus 4 additional injections in the arsenical intermission that is employed in the 30–60–03 scheme, the remaining bismuth injections to complete the 80-week standard being continued in 10-injection intermittent courses after the completion of the arsenical phase of treatment.

Dosage of Arsenicals.—In this scheme mapharsen is given in average individual doses of 60 mg. Neoarsphenamine, which is much less employed nowadays in the United States than formerly, is given in average dosage of 0.6 to 0.75 Gm., rarely going as high as 0.9 Gm. The more slowly one injects neoarsphenamine intravenously the better, but mapharsen can be injected as rapidly as one wishes; indeed, from the standpoint of preventing pain from venous spasm, the faster the better. Since mapharsen becomes less toxic on exposure to air, agitation of the solution during preparation is desirable; it also seems that no loss in therapeutic efficacy is suffered if such a solution is allowed to stand several hours before use.

Bismuth Dosage.—In this conservative type of treatment it is customary to administer about 100 mg. (0.1 Gm.) of metallic bismuth weekly. In the United States I think the most customarily employed measure by which this is accomplished is to give one injection weekly of a suspension of bismuth subsalicylate in oil, injecting either 1 or 2 cc. of such suspension depending upon its metal content. Of course the liposoluble preparations and the water soluble salts also have their advocates and are much used in comparable dosage: bismocymol, bismuth ethyl camphorate, bismosol, bismuth sodium tartrate, bismuth and potassium tartrate, thio-bismol, iodobismitol with saligenin or with benzocaine. However, the water soluble preparations oftentimes cause considerable pain upon injection and they must be given two or three times weekly; some of the liposoluble preparations must be injected twice weekly also. Sobisminol mass, which may be taken by mouth, has not been very much employed; in Barnett and Meininger's (1945) series of patients about one-third had gastro-intestinal disturbances and in 6 per cent of the cases these were severe enough to necessitate discontinuance of treatment. The most serious objection to sobisminol mass, however, is the fact that there is no way of insuring that the preparation is taken regularly since one has only the word of the patient to rely upon.

Bismarsen.—This, a combined bismuth-arsphenamine salt which is given intramuscularly, was reported by Beerman *et al.* (1943), upon the basis of a very extensive experience extending over a number of years, to have a lower spirillicidal action and to effect healing more slowly in early syphilis than other arsenicals but nevertheless to have an excellent effect in preventing progression, neurosyphilis and relapses of all types.

Clorarsen.—Of the several new organic arsenicals which are having a trial in syphilis nowadays the only one which has been Council-accepted at the time of this present writing is clorarsen (dichlorophenarsine hydrochloride). It seems to me that not sufficient experience has been had with this agent as yet to warrant the description of its methods of employment in this book.

Precautions to Be Observed with This Type of Treatment.—Before starting the arsenical course careful physical examination and urine analysis should be made, and the patient's full history elicited in order to determine whether one or more of the following conditions obtain. Evidence or history of skin hypersensitivity (chronic urticaria, eczema, seborrheic dermatitis, frequent "rashes") will indicate the necessity of starting with much lower than usual doses. There is evidence that untreated syphilis adversely affects the course of pulmonary tuberculosis and that treatment of the syphilis checks the progress of the tuberculous process (Smith, 1938; Goldblatt, 1939). The impression has been that a precautionary lowering of arsenical dosage is advisable and that if the tuberculous state is far advanced and cachectic, bismuth had best at least begin the treatment; yet Smith, who began treatment on this principle in the earlier cases in his series of 69 double infections, increased his dosage up to just about adequate for uncomplicated syphilis toward the end. If the patient is pregnant, is jaundiced, or has a liver or cardiovascular involvement, see the sections dealing with these conditions later in the chapter. Riddell and Anderson (1944) found impairment of liver function in a significant proportion of patients receiving arsenical treatment for syphilis and that, since this impairment bore no relation to the total quantity of drugs given and was attributable to individual sensitiveness to the arsenicals, the institution of routine hippuric acid tests during treatment with arsenicals would be found worthwhile wherever its employment is practicable. In hyperthyroidism, Stokes (1934) found such explosive reactivity to the arsenicals that he preferred to control the hyperthyroidism before beginning antisyphilitic therapy. History of marked easy "bruising" should make one very cautious in the use of arsenicals, and evidences on mucous membranes or skin (or reliable history) of purpura is probably sufficient to contraindicate the use of these drugs; tendency to lightly induced and prolonged hemorrhage should also be taken as warning of delicate balance in the blood-forming mechanisms. Mild nephritis counsels caution and initial dosage reduction and so does mild diabetes; untreated diabetes, especially if acidotic, had better be controlled before the arsenical treatments begin, unless the patient is in the advantageous seronegative primary stage of syphilis, which will warrant beginning both treatments simultaneously. Primary anemia necessitates dosage reduction in the beginning, but secondary anemia is usually quickly benefited by the arsenicals; arthritics and hypertensives are often helped. Optic or acoustic nerve involvement necessitates preparatory use of a heavy metal for three to six weeks (Stokes, 1934). Constipation not infrequently disappears during treatment, since the arsenicals tend to induce moderate diarrhea; it is customary in the practice of some men to have a saline cathartic taken on the morning after each injection.

The meal preceding the injection of an arsenical and the next one following it should consist of nothing more than toast and coffee or tea, and nothing at all should be placed in the stomach for at least two hours before the injection. It is the almost universal custom to place the patient on a high carbohydrate and low fat and protein diet, usually accomplished by forcing the taking of much bread, potatoes, and cereals through a great restriction in the allowance of meat, fish, eggs, milk and butter, the belief being that the liver is thus to some extent protected against the hepatotoxic action of the arsenicals.

Cooperation Required of the Patient.—The perfectly cooperative patient will comply with the following requirements: (*a*) Abstain not only from sexual intercourse but from all physical contact with other individuals or any articles

whatsoever—pipes, towels, shaving paraphernalia, etc.—in use by others. (*b*) Dishes to be scalded after use. (*c*) Burn all dressings. (*d*) Take good care of the teeth and when visiting dentist tell him of the infection. (*e*) Abstain from smoking and drinking (the harmfulness of tobacco in early syphilis is not proved but since smoking may predispose to dangerous leukoplakia at a later period, it is as well to attempt to break the habit in the beginning; alcohol probably harms principally by increasing the likelihood of occurrence of arsenical reactions, as well as inducing a lowering of the bars of caution). (*f*) Live as calmly and quietly as possible consistently with obtaining requisite moderate exercise. The considerable importance of obtaining plenty of sleep and the relief from tedium afforded by an occasional vacation was reemphasized by Obermayer and Becker (1936). (*g*) Report pimples, hemorrhoids, coughs, colds, all other illnesses and indispositions to the physician.

Marriage.—Syphilis has been contracted from individuals who had neither clinical nor serologic evidences of the disease. Nor is the fact of adequate treatment always a guarantee of protection; Lunsford and Day (1934) infected rabbits by lymph-node tissue transplantation from 3 patients who had received continuous and intensive treatment from the beginning of their infection and for periods of eighteen, thirty and thirty-six months, respectively. Therefore the physician can never guarantee that a patient is completely noninfectious. Can the young syphilitic, healthy save for his infection, never marry then? He is going to do so of course, but when may this take place with greatest safety for his wife and future children? The most lenient of all the answers to this question provided by those who can speak authoritatively is that of Moore (1933): "Sexual intercourse is permitted after the sixth month of treatment provided that (*a*) the patient wears a condom and (*b*) that intercourse occurs during the arsphenamine phase of therapy. As to marriage and unrestricted sexual intercourse, continuous treatment for twelve to eighteen months, during the last year of which the patient is seronegative, after which marriage may be permitted." On the basis of their study of conjugal syphilis at the Mayo Clinic, and writing of syphilis *per se* without any relationship to the amount of treatment received, O'Leary and Williams (1940) said the disease may be considered to be infectious during the first five years but that each year thereafter the possibility of the individual transmitting it decreases until it approaches a vanishing point by the tenth year. I wonder if the above are still going to be our opinions after a few more years' experience with the intensive types of therapy?

Arsenical Reactions

It should be noted that all the reactions discussed below, with the exceptions indicated, occur much less frequently with mapharsen than with neoarsphenamine or bismarsen; in a statistical review of the toxic effects of arsenical compounds in the United States Navy, Stephenson *et al.* (1942) reported that reactions of any sort occurred only one-third as frequently following mapharsen as following neoarsphenamine. It seems that the nitritoid reaction does not occur with mapharsen at all, at least Levin and Keddie (1942) were unable to find a report of a case of true nitritoid reaction in their thorough study of the literature.

Nitritoid Reaction.—This type of reaction (not seen with mapharsen) usually begins shortly after the neoarsphenamine injection has been started or the bismarsen has been placed in the buttock. There may be sudden intense pain

in the back though this is very rare; always, however, there is a quick general or blotchy flushing of the face and neck and injection of the eyes, dyspnea, cough, nausea and anxiety; sometimes, though unusually, the patient vomits at this point; usually the pulse becomes momentarily bounding and then very weak and edema of the face and neck may supervene. Sometimes there is loss of consciousness with suspended respiration for a few seconds. The symptoms usually persist for half an hour in some degree, sometimes longer. Though frightening to witness, the nitritoid reaction is fatal only in extremely rare instances. The often fatal colloidoclastic shock, with somewhat similar symptoms, which occurs as the result of faulty preparation or administration of old arsphenamine, need not worry the practitioner using neoarsphenamine or bismarsen, but he should be prepared for the patient's thorough fright through one such nitritoid experience, and he *must* heed the instructions for preparation and slow administration if he is to avoid frequent occurrence of this type of reaction with neoarsphenamine.

About the only effective treatment for the nitritoid reaction is the immediate subcutaneous or intramuscular injection of 0.5 to 1 cc. of epinephrine hydrochloride (adrenalin) 1:1000 solution—the arsenical injection having been stopped, of course. It is sometimes possible to prevent the recurrence of this reaction by the subcutaneous injection of 1/75 to 1/50 grain (0.0008–0.0012 Gm.) of atropine sulfate fifteen minutes before the injection; or epinephrine may be given before the injection instead of after the symptoms have appeared. Ephedrine sulfate is sometimes used, several doses of $\frac{3}{8}$ grain (0.025 Gm.) by mouth on the day before and the day of the injection. Whether or not the stuffing of arsenic-sensitive patients with vitamin C has preventive value is not yet determined since the literature is very conflicting, but Beerman *et al.* (1943) seemed to have produced evidence that the administration of the arsenical in an ascorbic acid solution possibly has some value. To 114 patients who had previously had bad reactions they gave the arsenicals in an aqueous solvent containing methyl glucamine ascorbate in doses equivalent to 60, 100, or 500 mg. of ascorbic acid and 7 per cent sucrose; about half the patients seemed to have been benefited, the solvent containing the 100 mg. dose apparently having been especially useful.

Lacrimation-Salivation Reaction.—A reaction apparently peculiar to mapharsen consists in mild lacrimation with mild to profuse salivation, beginning fifteen minutes to three hours after injection and lasting several hours. The reaction seems to be annoying rather than truly distressing and does not often occur.

Gastro-intestinal Reactions.—Many individuals are much disturbed by an "etherlike" odor and disgusting taste while neoarsphenamine is being injected. This may be counteracted by causing the patient to smell bay rum or a perfume during the operation (the cheaper perfumes are preferable because of their greater pungency); place on a pledget of cotton and not on the clothing in order to avoid later embarrassment to the patient. Some individuals derive equal comfort from the rapid mastication in quick succession of several pieces of fresh wintergreen chewing gum.

When stomatitis occurs during arsenical administration it is almost always of a dry red type, usually accompanied by chapping of the lips, and hardly to be confused with the stomatitis of bismuth or mercury. Its chief significance is that it may be a warning of idiosyncrasy for the drug which will eventuate in serious dermatitis or hematopoietic damage if administration is persisted in.

Occasionally a patient will have more than the three or four stools which often follow in the few hours after the injection of an arsenical, and it may be necessary to give a dose of castor oil or very rarely an opiate. Milk toast, made from boiled milk, for several meals succeeding the injection usually suffices to check the trouble in patients who have this diarrheal tendency. The drug effect is not lost by reason of these loose stools. Severe gastro-intestinal complications, such as the fatal neoarsphenamine gastric necrosis reported by Christianson (1935), are extremely rare. The rubber tubing type of reaction, which has a gastro-intestinal phase and is of serious moment in clinics where old arsphenamine is administered, does not concern us here.

Many physicians have found their patients experiencing fewer gastro-intestinal reactions under mapharsen than under neoarsphenamine. Levin and Keddie (1942) said that about 90 per cent of patients who have severe gastro-intestinal reactions to the arsphenamines can tolerate mapharsen in therapeutic doses.

Skin Reactions.—Urticaria or a scarlatiniform erythema often occurs during the nitritoid reaction and subsides with it. Or such an eruption, accompanied by fever but not associated with nitritoid phenomena, may be experienced following one of the early injections, ordinarily not recurring. These fleeting skin involvements do not usually require any treatment. Generalized itching unaccompanied by dermatitis and following upon the injection of an arsenical is generally looked upon as a warning signal that further arsenical treatment if given at all should be under the supervision of a specialist. Interest in what is known as "ninth-day fever" in Europe was revived in this country by Keim (1935): scarlatiniform or morbilliform eruption occurring on the eighth to twelfth day after one of the early injections, together with chill and fever, pharyngitis, vomiting, pains throughout the body, superficial adenopathy and perhaps photophobia as in measles. There may also be subsequent desquamation as in scarlet fever. The reaction is nearly always over in five to seven days, but Muir (1937) reported a case which was followed by severe neuritis and later by severe vesicobullous dermatitis and death from toxic degeneration of internal organs. In Robinson's (1938) case, which developed after the third injection of neoarsphenamine, treatment was stopped for two weeks; upon its resumption after full recovery of the patient, hepatitis and jaundice developed very promptly. He, as well as Epstein and Levin (1939) and Canizars and Thomas (1939), reporting 6 and 11 cases respectively, felt that arsenical treatment should be resumed with caution after one of these reactions, the first dose being reduced in quantity. I have already mentioned the fact that the occurrence of this ninth-day type of reaction is also considered to contraindicate further administration of the arsenical during the course of a ten-day multiple-injection intensive type of treatment (*q.v.*). There is also occasionally seen a "fixed" type of eruption which does not contraindicate continuance of treatment: one or more plaques which redden and swell, perhaps even become bullous, following each injection; residual pigmentation fades very slowly. Mendelsohn (1940) reported an interesting case in which sharp pain in the jaw recurred with each fixed eruption.

If to this brief sketch is added the occasional herpes zoster or lichen planus or erythema multiforme type of eruption and the very uncommon eczematous weeping eruption, practically all of the skin involvements will have been covered except the most important one—exfoliative dermatitis, which accounts for many of the deaths occurring with the more conservative types of anti-

syphilitic therapy. This reaction may occur at any time in any individual, but the 4 fatal cases observed by the Cooperative Clinical Group were in young people with early syphilis and the reaction appeared after the third or fourth injection. Briefly, the entity has the following characteristics: (*a*) general flush, with dry or moist dermatitis of flexor surfaces and lower parts of the body, accompanied by very severe itching; (*b*) usually some degree of edema and a septic temperature; (*c*) practically always a sensation of great chilliness; (*d*) the full picture may be established in a few hours after an injection, and death may occur very early with intercurrent respiratory or myocardial symptoms; (*e*) the patient may linger many weeks or months, with the skin becoming very scaly and secondarily infected, the body wasting away (Cannon *et al.*, 1942, redirected attention to the interesting poikiloderma-like changes which occur ultimately in extremely rare instances), liver, kidneys, intestinal tract and bone marrow becoming involved, and death finally occurring through these complications or an intercurrent pneumonia. Any general practitioner having the misfortune to have a patient develop exfoliative dermatitis will certainly make every effort to get him into a hospital and to have specialist consultation. The chief elements of treatment seem to be the following:

(*a*) The use of the alkaline colloid bath, as described under Eczema-Dermatitis. Be sure to get the bland ointment on quickly after removal from the tub else misery will only be increased by these baths.

(*b*) Under Eczema-Dermatitis are described measures useful in the early stages of a dermatitis; Stokes warned against the use of any directly antipruritic agents, such as phenol, which he felt always aggravate these cases of arsenical dermatitis. Hollander (1936) employed 5 per cent aqueous solution of tannic acid, either sprayed all over the body or applied as a wet dressing, with satisfaction.

(*c*) Use warm saturated boric acid solution for syringing ears and bathing eyes; argyrol (10 per cent) if the conjunctivitis becomes purulent.

(*d*) Do everything possible to dissuade the patient from scratching and to prevent secondary infection—clean linens and bedclothes and thoroughly cleaned tub.

(*e*) Keep up nutrition as well as possible, both for constitutional protection and as safeguard against development of bed sores.

(*f*) Sodium thiosulfate: After a thorough review of this subject in 1942, the Council on Pharmacy and Chemistry of the American Medical Association reached the conclusion that sodium thiosulfate is of no value in the treatment of arsenical or other heavy metal intoxication; and I shall therefore no longer describe this type of treatment.

(*g*) To discontinue arsenical treatment should certainly be the rule for the general practitioner; whether it may be cautiously resumed in a given case is a question to be answered only by the experienced specialist in close touch with the patient. Schoch *et al.* (1940) believed, as a result of considerable study, that mapharsen can usually be successfully used in patients after recovery from dermatitis produced by neoarsphenamine but only if the dermatitis has been of lesser severity than severe exfoliative dermatitis necessitating hospitalization; they recommended that mapharsen dosage be begun at 1 mg. and be very gradually built up, *i.e.*, requiring 10 to 14 injections to reach a 40 to 60 mg. dose.

Unfortunately, a patient who has survived an arsenic-induced exfoliative

dermatitis may be plunged into a second attack by the use of any of the other antisyphilitic drugs.

(*h*) Jenkins (1943), of the U.S.P.H.S., believed that histamine therapy hastened the recovery of the 6 patients in which it was tried The first dose was of 0.1 cc. of 1:1000 histamine dihydrochloride solution administered subcutaneously, with epinephrine in a syringe close at hand in the event of a severe reaction; if the first injection was well tolerated the patient was given 0.5 cc. subcutaneously every other day until he had fully recovered. No reactions sufficiently serious to cause the routine to be changed were observed in this small series of cases.

Hepatic Reaction.—Around the pleasant little point of jaundice and hepatic injury in syphilis there has been spinning a considerable difference of opinion almost continuously since the arsphenamines came into general use. It seems to me that the studies of Wile and Sams (1934), Sager (1936), Hahn (1943), Mitchell (1943), Ottenberg and Spiegel (1943), Beattie and Marshall (1944) and Riddell and Anderson (1944), most notably among numerous others, have established the following points with reasonable assurance of their truth:

(*a*) In a certain exceedingly small proportion of individuals with untreated secondary syphilis, jaundice appears merely as one of the evidences of the generalization of the early toxemia.

(*b*) In individuals undergoing treatment with one of the arsenicals, this symptom occurs with much greater frequency, particularly if the drug is neoarsphenamine rather than mapharsen.

(*c*) In most instances the fully developed clinical picture so closely resembles the familiar one of infectious hepatitis (catarrhal jaundice) as to make differentiation of the two conditions impossible save on the basis of history alone.

(*d*) The onset of symptoms may take place at any time during, or as long as ten months after, completion of the arsenical course.

(*e*) In a small proportion of the cases full acute yellow atrophy of the liver develops: suddenly developing chills and fever, abdominal pain and liver tenderness, vomiting, delirium, prostration, coma, death.

(*f*) In neither syphilitic cirrhosis, diffuse hepatitis, nor hepatic gumma—which are generally looked upon as the "typical" forms of anatomic tertiary syphilis of the liver, though Hahn's (1943) analysis of the anatomic findings in 66 autopsied cases of late hepatic syphilis revealed almost exclusively findings of a focal gummatous nature—does this picture develop.

(*g*) The syndrome is not merely a type of Herxheimer reaction, as might be suspected in instances when it appears following one of the early injections; nor is it the mere recurrence of active syphilis affecting the liver only (hepato-recurrence), as has been contended when it occurs following a lapse in treatment.

(*h*) It does not merely represent the coincidental occurrence of infectious hepatitis in a patient with syphilis, though admittedly the contention of Bigger (1943), and Salaman and King (1944), is arresting; to wit, that jaundice in syphilitics under treatment is probably just the familiar infectious hepatitis transmitted from one patient to another by insufficiently sterilized syringes.

(*i*) It is caused fundamentally by the toxic action of the drug on the liver.

Nowadays it is sometimes considered advisable to continue treatment in the presence of jaundice which has appeared after the administration of an arsenical, the picture clearing slowly while treatment is being continued; but this is certainly dangerous procedure for the general practitioner, and I think

that he is still well advised to discontinue the use of arsenic in any patient becoming jaundiced, unless he has the advantage of studying his case in consultation with a skilled syphilologist. In combating the liver injury itself, carbohydrates are usually pushed. Soffer (1939) gave 400 to 600 Gm. daily and employed the continuous intravenous drip of 5 per cent dextrose if the high carbohydrate diet was not well accepted. Appel and Jankelson (1935) favored the frequent intravenous injection of 10 cc. of 5 per cent sodium dehydrocholate (decholin), but there has certainly not been general acceptance of this therapy; Soffer agreed with Ottenberg (1935) that to give choleretics in postarsphenamine hepatitis has no more rationale than the use of diuretics in acute nephritis.

If the patient presents with jaundice, *i.e.*, in the presence of early syphilitic hepatitis with jaundice in an untreated patient, Stokes advised preparatory treatment with bismuth for three to six weeks before instituting arsenical therapy; certainly most men agree with and follow the practice but the number of such cases is not large and therefore we have no real assurance that arsenicals begun in small dosage would be more harmful than bismuth. Despite the fact that Leonard's (1944) patient, presenting with jaundice, died of acute yellow atrophy after 3 injections of mapharsen and 2 of bismuth, she felt that the literature supports the stand that the use of the arsenicals in the treatment of jaundice in acute syphilis is justified, for she was able to collect the reports of 31 cases of syphilitic hepatitis with jaundice in which arsenical therapy brought about rapid clearing. Forbes (1944) compared the results in 10 patients who received bismuth during the jaundice with those in 11 patients given no treatment at all and felt that they supported the use of bismuth; but I thought that his findings were quite inconclusive. It furthermore seems to me that much more work must be done before one can accept the suggestion of Beattie and Marshall (1944) that the sulfur-containing amino acid, methionine, be used as a dietary supplement as a prophylactic measure against jaundice.

Hematopoietic Reactions.—Fortunately, in view of the extremely high fatality rate, arsenic injuries to the blood-forming apparatus are rare. McCarthy and Wilson's (1932) review established the vast majority of cases as being classifiable as follows: (*a*) thrombocytopenic, with typical purpuric or external hemorrhagic features; (*b*) granulocytopenic, presenting the picture of a fulminating agranulocytosis; and (*c*) aplastic, with the characteristics manifested when all the cellular elements of the blood have been affected. Symptoms may appear after any injection in any one of the courses. Bronfin and Singerman (1932) recommended frequent blood examinations in every patient under treatment with any of the arsenicals even in the absence of untoward manifestations, and the immediate discontinuance of the drug as soon as such symptoms as malaise, pallor, itching of the skin, or purpuric signs are noted. The consensus has certainly been until recently that no arsenicals should be given to a patient who has manifested in a severe form any of the hematopoietic types of reaction; however, since mapharsen causes reactions of this type much less frequently than neoarsphenamine, there have appeared a few studies in which the newer drug was successfully substituted for the older in most instances. For example, the experience of Epstein and Falconer (1940) indicated that mapharsen usually will not cause a reproduction of the purpuric reaction in patients exhibiting this type of dyscrasia; and there are also indications from scattered case reports that mapharsen can often be safely sub-

stituted for neoarsphenamine in individuals who have experienced an attack of agranulocytosis from the latter. Nevertheless, one must weigh in the balance also the fact that there are single case reports of fatal blood dyscrasias following the use of mapharsen (Rein and Wise [1939], Rangiah [1940], Kirkham and Perlmutter [1941], Creswell and Roth [1941] and Freeman [1944]).

Nervous System Reactions.—These reactions occur extremely rarely with the conservative type of therapy under present consideration; they are therefore discussed more fully with the reactions seen in the more intensive types of treatment.

Herxheimer Reaction ("Therapeutic Shock").—This consists in a lighting up of all the syphilitic lesions, appearing in early syphilis from a few hours to a day after the first injection of an arsenical—perhaps more abruptly with mapharsen than with neoarsphenamine or bismarsen. The reaction disappears slowly during several succeeding days and very rarely recurs following subsequent doses. "Herxheimer" is usually of little moment in early syphilis because of the nature and location of the lesions; in late syphilis with its numerous visceral lesions very grave symptoms may accompany such a reaction—which fact often dictates therapeutic approach to late syphilis through preliminary use of heavy metals.

Prevention of Subsequent Reactions.—The findings of the Cooperative Clinical Group—which, be it noted, were reported before much experience had accumulated with mapharsen—may be summarized as follows:

(*a*) If treatment is continued and no precautionary steps are taken at all, 61 per cent of individuals will react again.

(*b*) If it is imperatively necessary to continue arsenical treatment, changing the drug is the most successful method of avoiding further trouble; only 35 per cent of the patients will again react.

(*c*) Next best to changing the drug is merely to reduce the subsequent doses; 45 per cent will react.

(*d*) The absolutely best assurance of avoiding a further reaction at any time is to postpone the next dose, if this is feasible, at least a month, preferably three to six months; after such postponement neither changing the drug nor reducing the dose seems to give any added advantage.

Detoxifying Agents.—Doak (1941), of Johns Hopkins, reviewed the subject of all the agents supposed to have a detoxifying effect when administered with the arsenicals; his conclusion was that none of them has been shown to have established worth.

Capillary Resistance Test.—The studies of Horne and Scarborough (1941) indicated that intolerance to arsenicals may be associated with decreased capillary resistance. I have not seen a report of the confirmation of these observations upon a large scale, but since the performance of a Rumpel-Leed test requires but a few moments it would seem advisable for the practitioner to avail himself of this possible aid to differentiation of sensitive from nonsensitive patients.

Accidental Paravenous Infiltration of Neoarsphenamine or Mapharsen.—Treat by withdrawal of needle and immediate injection from another syringe of 20 to 30 cc. of physiologic saline solution containing 0.5 per cent procaine hydrochloride (novocaine), placing the solution around and in the infiltrated area. Then complete the arsenical injection at another site. Cold compresses are usually helpful in the beginning; later, hot compresses of saturated solution of magnesium sulfate may be used.

Venous Spasm.—When injecting old arsphenamine, with which we are not concerning ourselves in this book, pain along the vein is sometimes observed during or immediately after injection. Such pain has been reported to occur not infrequently if mapharsen is injected *slowly*. An important point noted by Schoch (1936) is that cold, *not* hot applications, laid from elbow to shoulder along the anterior surface of the arm, will quickly stop this pain.

Bismuth Reactions

Though the reactions of a toxic nature which accompany the use of bismuth are many and varied, they are rarely severe enough when the intramuscular preparations are used to necessitate an interruption of the treatment for longer than a few days. The commonest of the symptoms is the appearance of a thin violaceous gray line on the gums, indicative of saturation; another symptom of a deleterious nature which is relatively often noted (but not nearly so often as with mercury) is stomatitis; it is usually of a mild sort and disappears promptly upon adjustment of the treatment schedule or dosage. Experience has taught that it is well to examine the urine of patients before beginning the treatments and to use the findings as a quantitative guide to the same. Now and then during the courses the urine even of patients having no preexisting nephritic disturbances will give evidence of a beginning toxic process in the kidneys, but this does not happen so often as with mercury and only rarely fails to disappear with adjustment in dosage or after a slight pause in treatment. Severe or long-lasting nephritis or nephrosis is rarely recovered, though Heyman (1944) was able to report the cases of 4 patients, seen in his hospital over a span of only a few years, in which the nephrotoxic action of bismuth produced an intensification of a previous renal insufficiency; in 2 of the patients the effect was temporary and a fair degree of renal function returned after several months, but in the other two death resulted. A few cases of anuria following a single injection are on record (the latest report I have seen is that of McClendon, 1941). Bismuth may induce diuresis and does so probably more markedly than and as often as mercury. Bismuth-induced Herxheimer reactions usually develop more slowly than those following arsenical medication.

The following occurrences are relatively rare: loss of ambition, asthenia, headache, pains in bones and muscles (bismuth "grippe"); gastro-intestinal disturbances, herpes zoster, purpura haemorrhagica, agranulocytosis, nitritoid crises, polyneuritis, various exanthemata and dermatoses (exfoliative dermatitis occurs, and erythema of the ninth day was seen twice by Goldman and Clarke, 1939), menstrual disturbances. Prior to Wolman's (1940) report of 2 cases of acute yellow atrophy, both in infants, ascribable to bismuth, no clear-cut instances of this serious type of damage had been described. However, Kulchar and Reynolds (1942) reported hepatitis as evidenced by jaundice occurring with the use of bismuth at the astonishingly high rate of 1 to 1030 injections; of course such a report, which is in complete variance with most previous experience, cannot be accepted until it can be proved that arsenic is not also responsible in the causation of many of these cases of jaundice or that some of the other factors discussed under hepatic reactions to the arsenicals are not operating. With the reactions of bismuth introduced intravenously we need not concern ourselves, since the introduction of the drug by this route is absolutely contraindicated. The frequent gastro-intestinal reactions to sobisminol mass taken by mouth have been referred to in an earlier section.

Mercury in the Treatment of Early Syphilis

The exhaustive comparative studies of mercurials, completed by Sollmann, Cole and their associates in 1935, excellently codified our knowledge of these drugs, but I do not feel justified in presenting a resume of their work here at this time because mercury in all forms has now practically been abandoned in favor of bismuth. A few of the principal preparations are still included here (see below), but what needs to be said about them can be accomplished very briefly. (*a*) In early syphilis about the only justification for using mercury is if the patient is so isolated that during his heavy metal periods he cannot visit or be visited by the physician at short intervals for bismuth injections and the physician does not wish to entrust him with sobisminol capsules to be taken by mouth. (*b*) Under these circumstances only the inunction method of administration is feasible, for mercury cannot be given intramuscularly through correspondence any more easily than bismuth, and the preparations available for oral administration are ineffective, often extremely irritating to the gastrointestinal tract and very prone to cause severe stomatitis and profuse salivation. (*c*) The mercury course should not be any shorter than the preferable bismuth course would have been, and it should if possible overlap the arsenical course at both ends; *i.e.*, begin the use of mercury a week before arsenic is discontinued and extend it for a week after resuming the arsenical treatments—this is important to prevent neurorecurrence during the first course especially. (*d*) If both arsenic and the next best drug, bismuth, are felt to be contraindicated in the primary attack upon a given case of early syphilis, as may very rarely happen, so that mercury has perforce to be used, the best procedure is to give daily intramuscular injections of either biniodide or succinimide; next best, mercuric salicylate, or the solution of colloidal mercury sulfide, either given intramuscularly twice weekly. (*e*) Mercury intravenously administered in early syphilis has made no place for itself as yet in this country. Mercury by inhalation and fumigation deserves no serious consideration. (*f*) Good care of the teeth and mouth probably aids considerably in preventing salivation. A mouth wash frequently used is the following:

℞	Tincture of kino	℥j	30.0
	Tincture of myrrh	℥ij	60.0

Label: Add a few drops of the mixture to an ounce (30 cc.) of water and use as mouth wash.

This mixture can be painted full strength on the gums if such special attention seems indicated.

Mercury by Inunction.—The preparation to use is the U.S.P. "stronger mercurial ointment," which contains 50 per cent of mercury in a suitable base. This is not "blue ointment," which contains, in the U.S.P.XII, only 10 per cent of mercury and is therefore less effective, nor is it "calomel ointment," which has no antisyphilitic value whatsoever. A dose of about 1 drachm (4 Gm.) is rubbed for thirty minutes into a different hairless portion of the body on each of six consecutive days, the site of inunction being previously washed with soap and water and then alcohol. A full bath with soap and water, but no rub, comprises treatment on the seventh day; on the next day the second course of rubs begins. This is a very effective way of mercurializing a patient but it is difficult to get him to persist in the timed rubs, and the procedure is a very dirty one and not easy to conceal from family and associates. A very simple method of cleansing the skin after an inunction is to wipe off the excess

ointment with benzine or naphtha, or very quickly with a good grade of leadless gasoline. In their earlier reports Cole and Sollmann stated that this cleansing does not lessen the effectiveness of the treatment, but in their later studies it seems that they have not entirely confirmed this impression. The United States Public Health Service has employed a belt or girdle on which the ointment is smeared. Dermatitis of various sorts may arise and cause temporary cessation of treatment but it is doubtful if absorption is affected by the skin disturbance.

Mercury by Intramuscular Injection.—For the practitioner who must occasionally inject mercury, the following 4 preparations will probably meet all needs. Both the *biniodide* (*red mercuric iodide*) and the *succinimide* are available in commercial ampules containing the adult dose, $\frac{1}{6}$ grain (0.01 Gm.). The injection is usually given daily and is often sharply but briefly painful. *Solution colloidal mercury sulfide* is usually given twice weekly in adult dosage of 2 to 3 cc. The injection seems to be quite painless, but sometimes an unsightly though harmless discoloration remains under the skin. *Mercuric salicylate* is commercially available in ampules containing 1, $1\frac{1}{2}$ and 2 grains (0.06, 0.09 and 0.12 Gm.) of the salt suspended in oils. The ampule must be immersed in warm water to liquefy its contents before use. Injections are usually made weekly and are rarely very painful at the time but there is not infrequently considerable and long-lasting pain which begins later. The adult dose is 1 to 3 grains (0.06–0.2 Gm.); Stokes said that less than 2 grains (0.12 Gm.) is almost certainly ineffective. Mercuric salicylate is slowly and irregularly absorbed and probably a considerable part of it is eliminated unchanged and without having exerted mercury effect; the only advantage which it possesses, in addition to being usually relatively painless at the time of injection, is that it is given less frequently than the other preparations.

Mercury by Mouth.—Inadvisable to use in early syphilis; the preparations are listed here merely because in the discussion of latent syphilis the reader is referred to this place for such a list. *Yellow Mercurous Iodide* (*Protoiodide*): The adult dose ranges from $\frac{1}{6}$ to 1 grain (0.01–0.06 Gm.), three times daily in tablet form; the average tolerated dose is perhaps about $\frac{1}{4}$ grain (0.015 Gm.). *Mercury with Chalk* (*Gray Powder*): Dose 1 to 4 grains (0.06–0.24 Gm.), three times daily in capsules, or the sweet powder may be taken as such. *Mercuric Chloride* (*Bichloride*): Dose 1/20 to $\frac{1}{4}$ grain (0.003–0.015 Gm.), three times daily. In my time at the New York Skin and Cancer Hospital this drug was combined with iodides in the following prescription for "mixed treatment"; the iron and strychnine are present in the hope of combating the anemia and anorexia that are frequently very prominent features in individuals being dosed with mercury (see below).

℞	Mercuric chloride	gr. iss	0.09
	Potassium iodide	ʒiv	16.0
	Ferric and ammonium citrate	ʒij	8.0
	Tincture of nux vomica	ʒij	8.0
	Water to make	℥iv	128.0

This preparation, which contains approximately 1/20 grain (0.003 Gm.) of mercuric chloride and 8 grains (0.5 Gm.) of potassium iodide to the teaspoonful, may be given in 1, or cautiously, 2 teaspoonful doses three or four times daily. *Red Mercuric Iodide* (*Biniodide*): This preparation may be dispensed in a bottle when rendered soluble by adding an equal quantity of sodium or

potassium iodide. The tolerated dose ranges between 1/20 and $\frac{1}{3}$ grain (0.003–0.02 Gm.); most patients can be safely started on 1/10 grain (0.006 Gm.).

Systemic Reactions to Mercury.—(*a*) Diuresis, occurring somewhat less frequently than with bismuth. (*b*) Renal disturbance of nephrotic nature, more frequent and severe than with bismuth. (*c*) Gastro-intestinal disturbances, even from preparations not administered by mouth: anorexia, salivation, stomatitis, colic and intractable diarrhea. (*d*) Anemia, wasting, polyneuritis, depression (even an occasional psychosis). (*e*) "Rheumatism," more severe than the "grippe" of bismuth. (*f*) Cutaneous reactions, other than the local disturbances associated with inunction, are rare.

Treatment of "Treatment-resistant" Syphilis

The truly treatment-resistant syphilitic is one in whom spirochetes, lesions, or serologic manifestations, or all three, are not typically affected by correct antisyphilitic therapy. The arsenicals are the drugs against which resistance is most often manifested, and most of the patients are early syphilitics, though resistance may be encountered in any stage of the disease. In the American cases recently described by Netherton (1937), Beckh and Kulchar (1939), and Templeton (1943), it did not seem that the trouble could be ascribed to infection with a treatment-resistant strain of organism; however, Beerman and Severac (1942) were able to demonstrate that the organism derived from one such treatment-resistant patient retained a certain amount of its characteristic resistance when it had been carried through many animal passages.

Prior to the advent of penicillin it had seemed to me that when the general practitioner encountered one of these rare cases the best thing he could do in the interest of his patient was transfer him to the practice of a competent syphilologist, who would probably: (*a*) run the gamut of the arsenicals; (*b*) try such minor drugs as the gold salts and sodium thiosulfate; (*c*) employ shock and fever therapy; (*d*) temporarily suspend all treatment under his expert and constant supervision. Now, however, Nelson and Duncan (1945) have reported 6 patients with treatment-resistant early syphilis in whom good results were obtained when arsenic and bismuth were abandoned in favor of penicillin—so apparently in this field, too, the great new agent is going to work its wonders.

Treatment of Latent and Wassermann-fast Syphilis

In this section we will be concerned with a certain type of patient recruited from the following classes: (1) those whose early syphilis was ignorantly or willfully not treated at all; (2) those whose early syphilis was inadequately treated; and (3) those in whom lesions of the primary and secondary stages were wholly absent or so slight and transient that opportunities for diagnosis and treatment did not present themselves. But not all individuals who for one reason or another did not obtain satisfactory treatment of their acquired syphilis fall within the present category, for a certain number of them will have earlier presented themselves with one or more of the lesions of late syphilis. The group is therefore whittled down to include only those patients whose sole manifestation of the disease is a positive blood Wassermann or Kahn reaction; such individuals are said to have "latent" syphilis. But be sure the reaction is not falsely positive; in addition to a large number of diseases in which it is not yet possible to estimate the incidence of transitory false positive reactions, Moore *et al.* (1940) said the probable frequency in yaws is 100 per cent, leprosy 40 to 80 per cent, malaria 100 per cent at some time during

the infection and infectious mononucleosis 20 per cent; the occurrence of such false positive reactions in the rickettsial infections has been mentioned elsewhere in the book.

Now what to do when a patient with true latent syphilis is detected? In the first place the thing *not* to do is plunge in, hurly-burly, to "clean him up" with intensive chemotherapy, for to do this may cause irreparable damage. The really proper lines of action I shall attempt to present briefly in what follows.

Search for Hidden Syphilis.—The patient should be thoroughly examined, with ophthalmologic, roentgenologic and other help as needed from specialists, to bring from below the subclinical level any occult syphilitic lesions which may be present. Once these are found, the therapeutic interest shifts to them and the Wassermann reaction merely becomes one of the several parts of the picture. Neurosyphilis, cardiovascular syphilis, hepatic, gastric, osseous and other miscellaneous manifestations of late syphilis are all discussed in sections of their own. These very serious cases disposed of through proper classification, which brings with it automatically the correct type of treatment, we must then decide for those which still remain in the latent class whether to treat them at all or not.

Course of Untreated Latent Syphilis.—If at the time of the diagnosis of latency the disease has existed four years so that the patient's own defensive mechanism has already become firmly established, the Cooperative Clinical Group found that the untreated course will be about as follows: (*a*) Ultimate spontaneous "cure" (negative blood and spinal Wassermann; no lesions), 25 to 35 per cent of patients. (*b*) Infection remains latent (positive blood but negative spinal fluid; no lesions), 25 to 35 per cent. (*c*) Late cutaneous, mucosal, or osseous syphilis, 10 to 15 per cent. (*d*) Cardiovascular syphilis, 10 to 15 per cent. (*e*) Neurosyphilis, 1 to 2 per cent. (*f*) Other visceral syphilis, 1 per cent or less. Repeated in other words, this means that even if left absolutely untreated 50 to 70 per cent of the patients (always with the proviso that their syphilis is four years old when latency is diagnosed) will grow no worse and about half of that proportion will actually achieve spontaneous "cure"; while about 20 to 30 per cent will develop visceral, cardiovascular, or some other form of late syphilis; and 1 to 2 per cent will eventually have neurosyphilis.

Course of Treated Latent Syphilis.—By proper treatment, the Group found it possible to achieve in 53 to 60 per cent of cases a result comparable to the spontaneous "cure" achieved in only 25 to 35 per cent of untreated cases, though it was admitted that unavoidable statistical errors may have allowed this figure to transcend the truth somewhat. But even so, it is apparent that an appreciably greater proportion of individuals with true latent syphilis will get rid of their infection if correctly treated than if left untreated.

Whom to Treat.—I must repeat here, since it is so important for the reader to bear in mind, that in all of this discussion we are concerning ourselves only with true latency, *i.e.*, individuals in whom the most searching examinations have failed to detect any evidence of the disease other than the positive blood Wassermann reaction. Such patients are divisible into two groups: "early" latency, with the full defense mechanism not yet established since the infection is less than four years old; and "late" latency, in which the patient has had time to develop completely his spontaneous resistance. It seems that practically always in "early" latency treatment should be instituted for the reason that such patients, being usually still quite young and sexually active, are a

social menace through their still considerable likelihood to develop infectious relapse; furthermore, the fact that they are not far removed in years from what was probably wholly inadequate arsenical treatment means that the occurrence of precocious tertiarism may still be expected in them. But in "late" latency the decision to treat or not to treat is more a matter of expediency. The studies of the Group revealed that the liability of a truly latent individual (*i.e.*, with a negative spinal fluid when the diagnosis is made) to develop neurosyphilis is extremely small. Also, if ten years have elapsed since infection and no evidences of cardiovascular involvement are found when the diagnosis of true latency is made, then such involvement is fairly certain not to occur later—though Stokes' reminder is an important one, namely, that the state of the small arteries of the brain, of the myocardium and of the coronary system is extremely difficult to appraise. It was clearly the opinion of Moore and of Stokes, and very probably of all the other outstanding syphilologists who comprised the Group, that an individual who is over fifty years of age, whose infection is of long standing and gives no more evidence of its existence than the positive blood Wassermann and a scar or two, such as a fixed pupil or an absent knee jerk—that such an individual is best left undisturbed by treatment, to come to death from causes other than his syphilis. (Mercury by mouth, or "mixed treatment" with mercury and iodides, has been much used in the past in such cases; but I believe that this kind of therapy might well be dispensed with entirely in our day.) In individuals younger than this each case must be more definitely weighed on its own merits. Stokes believes that the patient in his thirties or forties may still have time to "use up" all of his immunity and he therefore advocates treatment in all these cases. It is certainly true that some crippling degenerative process coming on many years after the primary infection may find such a patient still in his "best" years.

How to Treat.—The findings of the Group, as interpreted by Stokes *et al.* (1943), indicated that the best treatment of "early" latency is simply that of early syphilis, which means the employment of the "30–60–03" system which has been previously discussed. However, many observers believe that the course should begin with heavy metal to safeguard the patient against serious Herxheimer reaction in a lesion which the exercise of utmost diagnostic acumen has failed to reveal.

The findings of the group with regard to the treatment of "late" latency have never been entirely clear to me, nor can I say that the recent attempt of Stokes *et al.* (1943) to clarify these findings has been of much help. But there is available a very clear cut report of results obtainable and treatment used in late latency, namely that of Kahn and Becker, of the University of Chicago (1942), in which the satisfactory results obtained were better than those obtained by the Group, *i.e.*, 68.5 per cent as against 53 to 60 per cent. I therefore offer here in Table 8 Kahn and Becker's treatment outline for late latency, as kindly revised for me by Dr. Becker in November, 1944. It will be seen that the primary features of this treatment scheme are that it begins with bismuth, comprises several periods during which bismuth and mapharsen are being given simultaneously with rest and bismuth periods alone in between, and that it ends with bismuth after succeeding rest periods of increasing length.

Wassermann "Fastness."—From what has been said in this section I imagine it is apparent that the mere fact of a persistently positive blood Wassermann reaction is in itself not of fundamental significance. Some of these reactions are undoubtedly due to the refinements in present-day serologic

methods; some of them disappear spontaneously several months after cessation of treatments; some of them are increased in positiveness and possibly more firmly "fixed" by treatment. The thing of chief importance is to see that the latency itself, and not the Wassermann fastness, is assessed at its proper value and treated or not accordingly. If in a given case there seems to be reason for

TABLE 8.—TREATMENT SCHEDULE FOR "LATE" LATENCY

Weeks	*Mapharsen, mg.*	*Bismuth Salicylate, cc.*
1 to 10	.....	10 weekly injections, 0.5 to 2 cc.
	1 month's rest (optional)	
11	30	0.5
12	60	1.0
13	60	1.0
14	60	1.0
15	60	1.0
16	60	1.0
17	60	1.0
18	60	1.0
	1 month's rest	
22 to 29	.....	8 weekly injections, 0.5 to 2 cc.
	1 month's rest	
33	30	0.5
34	60	1.0
35	60	1.0
36	60	1.0
37	60	1.0
38	60	1.0
39	60	1.0
40	60	1.0
	1 month's rest	
44 to 51	.....	8 weekly injections, 0.5 to 2 cc.
	1 month's rest	
55	30	0.5
56	60	1.0
57	60	1.0
58	60	1.0
59	60	1.0
60	60	1.0
61	60	1.0
62	60	1.0
	3 months' rest	
74 to 83	.....	16 weekly injections, 0.5 to 2 cc.
	6 months' rest	
107 to 116	.....	10 weekly injections
	1 year's rest	
168 to 177	.....	10 weekly injections

If blood test is negative, place on observation; if positive, give one course of bismuth each year.

Iodides may be given throughout.

This schedule is for a healthy adult male, and the dosage of mapharsen should be slightly smaller for women; the bismuth dosage may remain the same.

attacking the fastness alone, the other indications having been satisfactorily met by treatment, then it seems to me that the general practitioner is well advised to turn his patient over to a specialist, who will likely attempt some such juggling as is employed in combating arsenic resistance, previously discussed.

Treatment of Early Neurosyphilis

The best that the general practitioner can do to safeguard his patient against the development of neurosyphilis at any time is to treat him most vigorously according to either of the intensive plans, or the Army (26 week) plan, or the standard or "conservative" plan of the Cooperative Clinical Group—all of which have been described in the discussion of the treatment of early syphilis earlier in this article. The occurrence of primary syphilitic meningitis, with any or all of the following symptoms, can be taken to mean that the individual is not being treated with enough intensity: headache, pain and stiffness in the neck, nausea and vomiting, mental signs, convulsions, cranial nerve palsies, aphasia, hemiplegia, increased cerebrospinal pressure, pleocytosis and a positive Wassermann of the fluid. Such an occurrence calls for hospitalization and intensification of the chemotherapeutic attack. Merritt and Moore (1935) found it of value during the acute period to drain off spinal fluid repeatedly until the fluid circulation is readjusted. Failure to respond to intensification of course necessitates resort to tryparsamide, intraspinal, or fever therapy. However, Nelson and Duncan (1945) have reported 10 cases of acute syphilitic meningitis treated with penicillin in which the immediate results were excellent both from the clinical and laboratory standpoints. This is amazing since penicillin does not appear in the cerebrospinal fluid after intramuscular administration as employed in this series. Nelson and Duncan believe that ideal penicillin therapy in such cases would be a total dose of 2 million to 3 million Oxford units administered intramuscularly every three or four hours day and night for eight to sixteen days.

The occurrence of such a syndrome as the above in the form of a true neurorecurrence, *i.e.*, the "lighting up" of dormant neurosyphilis during a lapse in treatment, will not be seen during the proper treatment of acute syphilis, even if one of the more conservative methods is being employed, provided the patient is cooperative. Precocious tertiarism, which may involve the nervous system, will also not be seen if the patient is being adequately treated.

If a patient who has been properly treated by any one of the several schemes nowadays available, and has been "cured" during the early stage of his syphilis, then later, after a period of probation, turns up with a seropositive spinal fluid it seems to be the consensus that it is best to approach the case as one of late neurosyphilis and treat accordingly (see below). And to have expert advice through consultation with a syphilologist is certainly the part of wisdom.

Treatment of Late Neurosyphilis

As late neurosyphilis I am considering here the occurrence of any of the following in a patient having latent syphilis: paresis and taboparesis; tabes dorsalis; optic atrophy; and meningovascular (cerebrospinal) neurosyphilis, including such widely separated entities as transverse myelitis, syphilitic epilepsy, brain gumma, late syphilitic hemiplegia, combined symptom disease and late asymptomatic neurosyphilis. Kierland *et al.* (1942), studying the results obtained in 2019 cases of neurosyphilis of all types, the material having been made available through the Cooperative Clinical Group, found: (*a*) The highest percentage of marked improvement together with the smallest rate of progression was observed among meningeal neurosyphilitic patients; (*b*) Tabetic patients showed both marked improvement and progression less frequently than paretic or taboparetic patients; (*c*) Marked improvement was observed with greater frequency when the spinal fluid reversed to negative

than when it remained positive in all types of neurosyphilis except taboparesis. In what follows below, the guiding principles of treatment will be supplemented by details of application of those measures only which can be feasibly employed by the nonspecialist.

Types of Routine Treatment.—Many men feel it advisable to begin treatment with a heavy metal, preferably bismuth of course, and to employ some iodide also; when arsenic is added later it should be given as intensively as possible. To accomplish this, the Cooperative Clinical Group treatment for early syphilis may be altered as follows: (*a*) Begin with a ten weeks' course of bismuth injected weekly, or perhaps preferably an eight weeks' course using preparations which may be injected twice or thrice per week. (*b*) Add arsenic in the last two weeks, injecting every five days if possible for a course of 10 injections. (*c*) The bismuth should overlap the arsenic again at the end, or it may be possible to continue it in half dosage throughout the arsenic period. (*d*) Give 3 to 5 such courses (one round of bismuth and arsenic constituting a course) and taking care to end with bismuth just as the beginning was made with bismuth. (*e*) Use iodides throughout, according to methods discussed on a later page.

The University of Chicago group (Walsh and Becker, 1941), whose favoring of the simultaneous administration of bismuth and arsenic in latent syphilis has been earlier discussed, were very pleased with their results in neurosyphilis with a routine about as follows: Five weeks of daily intramuscular injection of a soluble bismuth preparation together with daily intravenous administration of 25 to 100 cc. of 10 per cent sodium iodide solution (alternately, weekly injections of insoluble bismuth and iodides daily by mouth); four weeks' rest; six weeks of arsenic and bismuth simultaneously; four weeks' rest; eight weeks of bismuth; four weeks' rest; six weeks of arsenic and bismuth; four weeks' rest; eight weeks of bismuth; four weeks' rest; six weeks of arsenic and bismuth. What pleased them in their results was that they felt they were attained with less frequent resort to tryparsamide, intraspinal, or fever therapy than is necessary in the Cooperative Clinical Group method outlined above.

In the studies of Kulchar *et al.* (1940), it was shown that it is difficult to determine clinically whether any one bismuth preparation is superior to any other; Beerman *et al.* (1942) felt that bismarsen was an acceptable preparation in the treatment of neurosyphilis. It is well to remember that the Herxheimer reaction, with its typical intensification of symptoms, does occur even with bismuth therapy.

Intensification of Treatment by Use of Fever Therapy.—Some cases of neurosyphilis can undoubtedly be arrested if not actually cured by one or the other of the types of treatment discussed above; however, nowadays more and more patients are being given the advantage of fever therapy at the earliest possible moment and it seems not at all unlikely that all authorities in this field will soon be advising that all patients be treated by a combination of chemotherapy and fever therapy from the outset. In that type of therapy given the accolade of approval in the authoritative review of Simpson *et al.* (1942), the patient is given a series of fever treatments produced by physical means (felt by the authors cited as having by now been established to be superior to malaria therapy), an intramuscular injection of bismuth subsalicylate being given just before each fever treatment begins and an intravenous injection of an arsenical being given at the height of the fever. The fact seems to emerge out of the studies of several groups of workers that when the arsenical is employed in this

fashion mapharsen is superior to either neoarsphenamine, bismarsen, or even tryparsamide. Of course therapy by either the physical methods or through the induction of successive bouts of malaria is a highly specialized affair and requires that the patient be sent to an institution whose staff is trained in these technics; the induction of fever through the employment of typhoid vaccine, however, may be accomplished by the careful general practitioner in any hospital, and I therefore describe the method below.

Methods of Employing Typhoid Vaccine.—It should be understood that this sort of treatment is not to be given to patients of advanced age, to those with serious cardiac, pulmonary, or renal disease or with a severe degree of arteriosclerosis, and that a fever treatment is not to be administered during an acute upper respiratory infection if it may be avoided at that time. The older method of giving these typhoid vaccine fever treatments is to dilute 1 cc. of commercial typhoid vaccine containing 1 billion organisms to 10 cc. with physiologic saline solution and to keep this mixture in the refrigerator for use throughout the series of 10 to 16 reactions, treatments being usually given on alternate days. Using a tuberculin syringe for accuracy, doses of 10,000,000 or 15,000,000 organisms are given for the first 4 or 5 treatments and usually 15,000,000 or 20,000,000 for subsequent ones. The Nelson technic of giving a second injection at the height of the fever produced by the first is the one most usually employed. The first intravenous injection is given in the morning, the patient, who is well wrapped up in blankets, usually experiencing a chill within thirty minutes to two hours thereafter; this lasts for a few minutes and is followed by a rise of temperature. When the rise is well established and progressing, the second intravenous injection, using the same dosage, is given. The interval between the 2 doses should not be less than two hours. Temperatures of 105° F. (40.5° C.) to 107° F. (41.7° C.) may be obtained by this method but the temperature is not very reliably sustained and in some instances in order to obtain the desired temperature it is necessary to use larger dosage than that which I have stated, the patients in these latter instances experiencing an almost prohibitively severe chill.

In view of the shortcomings of the above method a newer way of giving the vaccine has been devised, namely, the continuous intravenous drip method. The use of this method was described by Knight *et al.* (1943), Cohen and Hale (1944), and Lawrence (1944), but I shall sketch briefly the method of Knight *et al.* since it was applied in by far the largest number of cases. The bed is protected by a rubber sheet over which a draw sheet is placed, the patient lies in it dressed only in a pajama coat, and a wooden frame is placed over him so that he may move about in bed without becoming entangled in heavy blankets which are placed over the frame and brought well down around his neck and his feet. The standard Army triple typhoid vaccine is used and is diluted for convenience 1:20 in 5 per cent dextrose saline solution. Directions for administration of the vaccine are then written as in the following sample:

$$30\ \mathrm{M} + \frac{300\ \mathrm{M} \times 1000\ \mathrm{cc.}}{60/\mathrm{m} \times 500\ \mathrm{cc.}}$$

Beginning at 7:00 A.M.

(M = million organisms; 60/m = 60 drops per minute)

This prescription indicates that at 7:00 A.M. the patient is to receive 30 million organisms from the stock solution and is then to be placed in bed under

the frame and blankets. At the end of one hour the intravenous drip needle is introduced into his vein and a solution diluted to contain 300 million organisms per 1000 cc. of 5 per cent dextrose saline is allowed to flow at the rate of 60 drops per minute until 500 cc. of the mixture has been given. It is said that the temperature will usually be observed to be rising at the end of two hours. Thereafter the patient's condition determines both the dilution and the rate of flow of subsequent infusions. For example if the temperature is not rising as it should, the following formula may be employed:

$$\frac{300\ \text{M} \times 1000\ \text{cc.}}{120/\text{m} \times 500\ \text{cc.}}$$

indicating that the same dilution is to be used but that the rate of flow is to be doubled and 500 cc. are to be given. If the desired response cannot be obtained by this means the concentration may be increased as in the following:

$$\frac{600\ \text{M} \times 1000\ \text{cc.}}{120/\text{m} \times 500\ \text{cc.}}$$

When the desired temperature is obtained the rate of flow is decreased; usually the concentration may remain unchanged as below:

$$\frac{600\ \text{M} \times 1000\ \text{cc.}}{30/\text{m} \times 500\ \text{cc.}}$$

Obviously the above is just the barest outline of a method which will require most careful and tedious application for its successful employment. The treatment is divided into three stages: (1) an induction period lasting from one to four hours, which consists of an afebrile and a febrile phase; (2) a period of therapeutic fever (over 104° F.) which usually may be prolonged as long as desired; and (3) the period of defervescence lasting one to two hours. Blood pressure is taken every half hour, temperature and pulse rate and volume every fifteen minutes. The patient is to take fluids by mouth in small amounts and may take such nourishing liquids as fruit juices and Coca Cola if desired. Excessive perspiration or fluid lost by vomiting is combated by intravenous infusion of 5 to 10 per cent dextrose saline solution. Usually an opiate is given to keep the patient quiet.

Of course there is no reason why bismuth and an arsenical should not be employed with this type of fever therapy as well as with the fever induced by physical means, and indeed Lawrence reported that he injected mapharsen at the height of the fever bout and gave bismuth intramuscularly twice weekly on days on which fever was not being induced.

Penicillin.—Toward the close of 1944 a very authoritative committee headed by Stokes, of Philadelphia, reported upon the results obtained by the use of penicillin in the treatment of 122 cases of neurosyphilis in a small list of the leading syphilis clinics in the United States. The highlights of this report were the following: (*a*) The abnormal spinal fluid improved in 74 per cent of the patients to some degree and to a considerable extent in 33 per cent. (*b*) Symptoms improved as follows: Simple demented paresis: In 30 cases on which data were adequate for classification, 80 per cent improved to some degree; nearly half improved 50 per cent or more, including 8 who improved 75 per cent and 1 restored to normal. Deteriorated paresis: Two of 10 improved 75 per cent, 1 improved 50 per cent, and in 7 there was no change.

Tabes dorsalis: One fifth of 14 cases improved 50 per cent or more. Of 7 with lightning pains, 2 were completely relieved, 1 improved 50 per cent, 2 improved 25 per cent, 1 unchanged and 1 worse. Of 7 cases of primary (?) optic atrophy, mostly advanced, none were made worse and 1 improved. In meningovascular neurosyphilis 40 per cent improved 50 to 75 per cent. (*c*) Herxheimer reactions (therapeutic shock) occurred sufficiently often as to elicit comment regarding their potential dangerousness; fortunately, however, they seemed controllable by reduction in dosage during the first twenty-four to forty-eight hours of an eight-day series without loss of ultimate effect. (*d*) Penicillin was administered according to two schemes: in the first, 25,000 units were given every three or four hours until 1,200,000 units had been given; and in the second, 25,000 to 50,000 units were given every two to four hours until 2,400,000 to 4,000,000 units had been given. There were no striking differences shown in the effects attainable with these two systems of dosage. (*e*) Previous treatment with arsenicals, bismuth and fever therapy did not appear to prepare patients for superior results with penicillin. (*f*) The durability of the good effect thus far observed, the possibility of complications from induced allergic response and disturbance of the immunity balance of the individual in latent and late syphilis, remain to be explored by larger experience and longer periods of observation.

The only comment I can make upon all of this is that the thing is amazing but that we shall have to allow considerable time to elapse before we can be sure that penicillin is really what this preliminary report indicates it may be in the treatment of neurosyphilis. Certainly the time has not yet come for the general practitioner to begin injecting this agent into all his neurosyphilitics.

Tryparsamide.—The drug is usually given intravenously in a dose of 30 to 50 mg. per kilogram (2.2 pounds) of body weight; the average adult dose of about 3 Gm. is dissolved in the ampule in 10 cc. of sterile, distilled water, and given at weekly intervals for eight to sixteen weeks, followed by a rest period of about six weeks. Many such courses are usually necessary to accomplish full results. The drug may also be given intramuscularly or subcutaneously, though it is often quite irritating under these conditions. Tryparsamide solutions should not be sterilized as this will cause an increase in toxicity, and the solution should be injected as soon as it is prepared. It is usual to give bismuth during the rest period. A fact which is being somewhat overlooked at present is that Lorenz *et al.* pointed out that their results were better when they gave 1 cc. of mercuric salicylate intramuscularly three days before each tryparsamide injection; some physicians are now giving full doses of either mercury or bismuth throughout the tryparsamide courses.

Nearly all patients gain considerably in weight and well-being while taking the drug. The most frequent complaint is of ringing in the ears and a feeling of being dizzy and dazed. Nitritoid reactions, nausea, vomiting and headache are of comparatively rare occurrence, and urticarial reactions, dermatitis and jaundice have been reported only a few times. Kopp and Solomon (1943) performed liver function tests on their group of 66 patients under tryparsamide therapy and found only a slight evidence of impaired liver function in 34 of them; they observed also that the administration of tryparsamide did not interfere with the improvement of liver function in patients in whom dysfunction had been induced by other types of therapy. It appears that tryparsamide occasionally activates mental and physical signs and symptoms in a most objectionable way.

Visual disturbances occur with sufficient frequency under tryparsamide therapy that the drug should be used only with the greatest care. Patients with preexisting optic involvement, such as contracted fields or abnormal fundi, are more liable to injury than normal patients; but since some of these patients experience a great improvement in their vision under treatment with the drug, its routine withholding in these cases is not warranted, though in such cases there should be expert ophthalmologic, and if possible syphilologic, supervision. The most important signs of adverse action of the drug on the optic tract are subjective dimness of vision, flickering or shimmering sensations, or flashes of light; also objective diminution in the visual acuity, contraction of the visual fields and changes in the fundi. The occurrence of subjective symptoms should be thoroughly investigated for an objective basis. If no objective signs are found, tryparsamide may be continued with caution. The presence of objective findings, traceable to the drug, is a contraindication to its further use for at least a month, after which it may be very cautiously resumed—but I repeat, this should all be done only with the most expert consultation available.

Swift-Ellis Intraspinal Technic.—One-half to one hour after intravenous injection of an arsenical, 40 cc. of blood are withdrawn into bottle-shaped centrifuge tubes, allowed to coagulate, centrifuged and placed in refrigerator. The following day 12 cc. of this serum are diluted with 18 cc. of normal saline and heated at 56° C. for one-half hour. After lumbar puncture the cerebrospinal fluid is withdrawn until the pressure is reduced to 30 mm. The barrel of a 20 cc. Luer syringe (which has a capacity of about 30 cc.) is connected to the needle by means of a rubber tube about 40 cm. long. The tubing is then allowed to fill with cerebrospinal fluid so that no air will be injected. The serum is then poured into the syringe and allowed to flow slowly into the subarachnoid space by means of gravity. Usually the serum flows in easily under even a lower pressure, but at times it is necessary to insert the plunger of the syringe to inject the last 5 cc. By the gravity method the danger of suddenly increasing the intraspinal pressure to the danger point, such as might occur with rapid injection with a syringe, is avoided. Pain in the legs, commencing a few hours after the injection, is more often noticed in tabetics than in patients with cerebrospinal syphilis. It can usually be controlled by means of phenacetin and codeine but occasionally morphine or dilaudid is required.

Kierland and O'Leary's (1941) contraindications to the employment of Swift-Ellis therapy are the following: (1) patients who exhibit the clinical signs of neurosyphilis which persist in spite of adequate treatment but in whom reactions to tests of the cerebrospinal fluid have become negative, (2) patients physically unfit, such as those who have advanced tabes dorsalis, (3) the presence of the signs and symptoms of advanced involvement and degeneration of the lower part of the spinal cord and (4) cases in which reactions from the treatment are more severe than those resulting from ordinary lumbar puncture.

Wassermann-fast Spinal Fluid.—Goodman and Moore (1935) studied this important subject and reached the conclusion that the rate and completeness of reversal of the abnormalities of the fluid cannot be used as the sole guide to the duration of treatment. Therefore in neurosyphilis, as in latent syphilis, Wassermann fastness has little significance as a detached phenomenon. More recently, Forman (1939), while agreeing with this viewpoint, felt as the result of experience in a relatively small series of cases that the pushing of chemo-

therapy, either alone or after fever therapy if the latter had been indicated, to the point of serologic reversal was worthwhile in the attempt to prevent relapse or progression.

Gastric Crisis.—The vomiting in syphilitic gastric crisis is central in origin, and the administration of cracked ice, carbonated waters, and the like has usually no effect upon it. The physician is therefore quite helpless in the presence of an abjectly miserable patient unless he turns to the sovereign remedies, morphine or dilaudid, which he often does. They control both the pain and the vomiting, but not infrequently must be used several times with the result that the patient sometimes has his tabes complicated by morphinism, a most difficult combination to treat. It is therefore of interest to note that McFarland a number of years ago reported favorably upon the rectal use of chloral hydrate and sodium bromide in these cases. In a series of 49 injections given to 12 patients he obtained in 76 per cent of the administrations fully as great relief as is obtained with opiates. He gave a retention enema containing in 15 cc. of fluid from 40 to 60 grains (2.6 to 4 Gm.) of each drug, depending upon the size of the patient. Unfortunately it would seem that this method is not readily applicable in all cases, since most patients receive several injections of an opiate during their first few attacks while a puzzled physician is trying to rule out gallstone colic, and so on.

Marinesco, Sager and Facon reported the use of 1 to 2 cc. of a 25 per cent sterilized magnesium sulfate solution intraspinally in this condition. In the 8 patients thus treated, pain and vomiting disappeared entirely in from thirty to fifty minutes after the injection. Some patients needed another injection after two or three days; in others the interval was lengthened to several months. Alajovanine and Horowitz (1932) used successfully intravenous injections of 1 to 3 mg. of atropine sulfate, once or twice daily, for several days. Fellows (1934) successfully employed forced spinal drainage, consisting of prolonged simultaneous intravenous injection of hypotonic saline solution (3000 to 3500 cc. of 0.45 per cent sodium chloride) and drainage of the spinal canal (withdrawal of 200 to 250 cc. of fluid).

Numerous surgical procedures have been proposed as a last resort; all of them have at least one success to their credit.

Lightning Pains.—The only hopeful therapy recently reported (except for penicillin which has already been dealt with) for relief of intractable lightning pains was the use of thiamine hydrochloride (vitamin B_1) intravenously in weekly doses of 10 mg. Metildi (1939) had treated only 6 patients and considered his report distinctly a preliminary one; but Cochems and Kemp (1942) found this therapy without value in the majority of their 26 patients.

Treatment of Cardiovascular Syphilis

Effect Upon Length of Life.—Once aortitis, the earliest of the lesions, has developed, the outlook is grave, but Cole and Usilton (1936), as spokesmen for the Cooperative Clinical Group, presented authoritative evidence of the following nature: with little or no treatment after detection of the lesion, the average duration of life was thirty-four months; with inadequate treatment, it was fifty-six months; with the use of much arsenical and heavy metal, it was eighty-five months. In the cases of saccular aneurysm, the length of life was increased through adequate treatment from thirty-seven to seventy-five months. In cases of aortic regurgitation, the average duration of life in the inadequately treated was forty months after diagnosis, which period was pro-

longed to fifty-five months when adequate treatment was administered. Latterly, Kampmeier and Combs (1940) analyzed 163 cases at the Vanderbilt University Hospital and decided that treatment does not favorably influence prognosis in aortic insufficiency; it will be very interesting to see how time resolves this difference of opinion.

What Constitutes Adequate Treatment?—In the old days when only mercury and the iodides were available it was felt that relief was sometimes afforded by their use in cardiovascular syphilis and that perhaps in isolated cases life was even prolonged. Then with the introduction of arsphenamine and its use in these cases in full doses without other preparatory treatment, there followed a sad period of many deaths caused in the following three ways: First, ventricular fibrillation, with sudden death during the injection. Second, death within twenty-four to forty-eight hours of an injection by sudden coronary occlusion or rupture of an aneurysm as the result of a Herxheimer reaction. Third, sudden congestive heart failure in patients not previously showing evidences of decompensation, these deaths being ascribed to the "therapeutic paradox" of Wile; *i.e.*, rapid replacement of healing inflammatory tissue in the myocardium, valves and aorta by contracting scar tissue, with the patient left functionally in much poorer condition than before treatment began. So arsphenamine was abandoned and mercury and the iodides fallen back upon again. Nowadays, as the result of cautious retrials with the less drastic neoarsphenamine and mapharsen in small doses, it has been found that if the use of these drugs is carefully preceded by employment of metals and iodides to promote slow resolution of syphilitic inflammatory tissue, the patient is very much better off than when treated without the arsenicals at all. The treatment scheme presented below is that of the Johns Hopkins investigators (see Moore, Danglade and Reisinger in Bibliography) and is fully representative of the type endorsed by the Cooperative Clinical Group. McDermott (1944), employing a slight modification of this treatment at the Cornell Medical College, could not observe any instances of Herxheimer or "therapeutic paradox" and felt that the only reactions observed were those common to the arsenical treatment of syphilis in general, though he felt that any patient with heart disease regardless of its etiology might not be able to tolerate one of the so-called minor reactions of arsenical therapy, such as vomiting or diarrhea, which would represent no great danger to a patient with a normal heart.

Treatment of Heart Failure.—If there is any evidence of congestive failure when the cardiovascular diagnosis is made, the patient is put at complete rest and digitalized, though of course the full effectiveness of this drug is rarely experienced in syphilitic heart disease. Unless there is persistent edema no other drugs are given except iodides; if there is edema, salyrgan intravenously, or succinimide of mercury intramuscularly, are given for a few days for their diuretic effect. Nitrites, xanthine vasodilators, and sedatives are employed when indicated. Convalescence is made purposely slow and subsequently graduated exercise is rigorously supervised. Ambulant patients are kept on maintenance digitalis dosage, continuously if necessary. Meanwhile when and if a fair degree of cardiac reserve is established, antisyphilitic therapy is begun.

Antisyphilitic Treatment.—Continuing the iodides, a start is made with bismuth, using preferably an insoluble suspension in oil because of its slow absorption and beginning with one-half doses. These doses are given every four or five days for 4 or 5 injections, and if tolerated, as is ordinarily the case, the full dose is then given once a week. The bismuth and iodide course is then

continued ten to twelve weeks before beginning the use of arsenic. If, on completion of the first bismuth course, the patient has not become completely ambulatory without edema or exertional dyspnea, bismarsen is considered the arsenical drug of choice. The intramuscular injections begin at 0.05 to 0.1 Gm. every five days and are increased later to 0.2 Gm. at four to seven-day intervals if no reaction has occurred. Twelve to 20 injections are a course. But if the patient is ambulatory with only slight signs of cardiac embarrassment at the end of the preparatory bismuth and iodide period, neoarsphenamine is used intravenously; nowadays of course many men are preferring mapharsen. The beginning dose of neoarsphenamine is 0.05 to 0.1 Gm., cautiously and gradually increased at weekly intervals to a maximum of 0.3 Gm., which may be only rarely exceeded; mapharsen is likewise reduced in dosage and given with equal caution. The course comprises 10 to 12 injections. Ideally, bismuth and iodide courses are alternated with arsenical courses without intervals for two years; thereafter, if the general physical condition is satisfactory, long rest periods may be instituted, but it is considered probably wise to give a bismuth course followed by one of bismarsen or one of the above arsenicals once yearly as long as the patient lives. The blood Wassermann reaction is usually "fast" and no attention is paid to it.

Whom Not to Treat.—Some patients of course never establish sufficient cardiac reserve to permit the use of an arsenical at all; in such the aim should be to alternate courses in which bismuth and iodides are used simultaneously with rest periods of two to four months or with courses of mercury by inunction. When it seems inadvisable to treat at all, because of advanced age, extremely poor condition, or the presence in advanced stage of a complicating disease, mercury may usually still be given by mouth with some slight effect, though the danger of adding to misery through induced gastro-intestinal disturbance must certainly be carefully weighed. Severe renal impairment precludes the use of both mercury and bismuth, and the arsenicals may not be used without heavy metal preparation; bismarsen may be cautiously tried. Complicating neurosyphilis may necessitate intraspinal treatment (for optic atrophy); only in instances of very great desperation would a trial of fever therapy be justified. Tryparsamide, however, does not seem to affect the cardiovascular lesion adversely.

Treatment of Syphilis in Pregnancy

The authoritative committee, comprising Cole, Jeans, Moore, O'Leary, Parran, Stokes and Vonderlehr, who prepared a statement on syphilis in pregnancy for the United States Public Health Service in 1940, made a statement which may be condensed as follows: only 17 per cent of the known conceptions in untreated syphilitic women result in living nonsyphilitic children; the remaining 83 per cent terminate in miscarriages, stillbirths, or living children with syphilis; 60,000 of these children with syphilis are born alive each year in the United States. Very obviously in view of this situation the obligation is to discover syphilis if it is present in the mother and then to treat *at* the fetus *through* the mother. Precisely the steps necessary in attacking this problem were indicated by the findings of the Cooperative Clinical Group a few years ago; in what follows a condensation of their report is interlarded with such recent material as is necessary to bring it completely up to date.

When and Whom to Treat.—In the syphilitic woman a negative blood reaction during pregnancy greatly increases the chances for a living, apparently

nonsyphilitic child, but it is insufficient to insure this happy issue since one tenth of the syphilitic children in the Group studies were born to mothers whose blood was negative during pregnancy. But disregarding the blood reaction, it is found that early and adequate treatment in pregnancy will result in 91 per cent of the women being delivered of apparently nonsyphilitic babies. The obligation is therefore very clear to examine thoroughly into the possibility of syphilis in the very beginning of pregnancy and to begin treatment as soon as a positive diagnosis is made or history obtained. Infection of the fetus probably rarely if ever occurs before the fifth month, so the more time there is for treatment before that period the less likely is the infection to take place. The clinical manifestations of syphilis are often suppressed during pregnancy and therefore routine blood serologic examination is most important. But a negative test early in pregnancy, even if coupled with a negative history, is not sufficient; syphilis may have been acquired after conception took place and therefore ideally, for complete safety, the test should be repeated at about the fifth and seventh months. McKelvey and Turner (1934) showed conclusively that even if syphilis is discovered late, treatment up to term will still considerably increase the chances of delivering a live, apparently nonsyphilitic child. Gammeltoft found some years ago, and the Clinical Group confirmed him, that the syphilitic mother may be delivered of a syphilitic baby many years after the infection, just as a syphilitic no longer capable of transmitting the disease in any other way may give it to another when acting as donor for a blood transfusion. Even a woman completely cured clinically and serologically will occasionally, if untreated, give birth to a syphilitic baby. The safest procedure therefore, considering that it is syphilis in the fetus which we are attempting to prevent, is for every woman who has or ever has had syphilis to take antisyphilitic treatment throughout each pregnancy regardless of her syphilitic status at the time.

Pregnant Woman's Tolerance of Arsenical Treatment.—Despite the fact that it may be fairly assumed that the kidneys and liver of the pregnant woman are already under some strain, the Group found that there is no significant difference in minor arsenical reactions in pregnant and nonpregnant women, and that the pregnant woman actually experiences fewer severe reactions. Ingraham (1939) questioned this, however, for in a statistical study over a five-year period in the Philadelphia General Hospital he found reactions to be more frequent in pregnant women, especially gastro-intestinal, renal and hepatic reactions. There are other observers, particularly abroad, who also maintain that susceptibility is heightened. Cole *et al.* (1940), in the statement above referred to, took the position that only toxic hepatitis and hemorrhagic encephalitis occur more frequently in pregnant than in nonpregnant women or in men. Thus it would seem that the subject of arsenical reactivity is *sub judice*.

Effect of Treatment on the Toxemias of Pregnancy.—Ingraham (see above) felt that antisyphilitic therapy may aggravate an existing toxemia or precipitate an incipient one. However, Peckham (1941), at the Johns Hopkins Hospital where vigorous therapy of syphilitic patients has been routine for many years, studied the matter in the records of 13,742 consecutive deliveries and definitely concluded that antisyphilitic therapy does not increase the incidence of the toxemias of pregnancy.

Type of Treatment.—Nowadays of course one must say something about the two types of treatment, the conservative and the intensive, and something about penicillin also.

Standard or "Conservative" Therapy.—If diagnosis is made early, treatment need not vary greatly from that of the charted outline in the discussion of early syphilis on a preceding page, regardless of the stage of syphilis in which the woman herself is thought to be. Cole *et al.* (see above) like to alternate 10 arsenicals with 8 bismuths right up to term, adjusting the overlap as may be necessary in order to end on arsenic; if the diagnosis is not made until late in pregnancy simultaneous treatment with arsenic and bismuth is advocated. They proposed the following rules: "(1) Always plan to give an arsenical for at least six weeks before delivery. (2) Try to administer at least 20 doses of an arsenical before delivery. If necessary administer mapharsen every five days or if very late in pregnancy twice a week." Ingraham, apparently somewhat nonplussed by the increase in arsenical reactions which he recorded (see above), raised the question whether more consideration should not be given to adequate preparatory heavy metal therapy before beginning arsenical treatment; this is certainly the opposite of what practically all other syphilologists are advocating and so far as I know has not yet been put to the test. Kennedy and Henington (1943), however, felt that arsenic should not be employed in the eighth and ninth months unless the patient has primary or secondary or otherwise active syphilis.

Intensive Therapy.—Rattner (1943) treated 27 pregnant women with syphilis with the intensive type of therapy employing both arsenic and bismuth concurrently during the five-day period (the details of these rapid treatment methods are given in the section on the treatment of early syphilis). The treatment was well tolerated by both mother and fetus regardless of the stage of the pregnancy or the duration of the syphilis whether primary, secondary, or latent. In no instance was there encountered a severe reaction or interference with the pregnancy. Twenty-five of these women gave birth to full-term, normal infants; 1 syphilitic infant was born to a mother who apparently had acquired a second infection while the infant was still *in utero*; 1 patient was lost from observation. In addition to this group 5 other patients who had been treated for early syphilis by the intensive method later became pregnant and gave birth to normally developed seronegative infants although further antisyphilitic treatment was purposely withheld from the mothers. In the series of 30 women treated by Speiser *et al.* (1945), 7 had to be classified as failures because their babies were certainly or presumptively syphilitic. One death from arsenical encephalopathy occurred in this group. A group of 32 women was also treated intensively before pregnancy by Speiser *et al.;* in this group there was only 1 failure, that of a mother who had a cutaneous relapse.

Penicillin.—Lentz *et al.* (1944) reported the treatment of 7 pregnant syphilitics with this agent. All of the mothers when observed at an average period of 260 days after treatment were clinically normal, 6 having been in secondary syphilis and 1 in early latent syphilis at the time of treatment; 4 of the 7 had become seronegative. Each of the infants had remained clinically and serologically normal for an average period of 124 days postpartum. These women had been given 1,200,000 or 2,400,000 units around the clock in approximately eight days, but it was felt that the larger dosage was to be preferred. In 2 of the women threatened abortion occurred and was attributed to a Herxheimer reaction in the placenta which it was felt could be avoided by a considerable reduction of dosage during the first thirty-six to forty-eight hours of therapy. This is a very small series from which to draw any conclusions, but it certainly seems that penicillin is likely to work its magic here also.

Treatment of Congenital Syphilis

Whom to Treat.—Usually the more recent the mother's infection and the less treatment she has had the more likely is the infant to be born with a mucocutaneous, osseous, nephritic, or other severe form of the disease which will take it off despite the most heroic chemotherapeutic and feeding efforts to save its life. But these cases do not pose the big problem in syphilis of the newborn, which is how to determine whether the apparently healthy baby of a treated syphilitic mother is itself syphilitic. Smith's (1935) reemphasis a number of years ago of the three periods in which lesions are most prevalent is still pertinent: (1) the first six months, when they are chiefly ectodermal, mucocutaneous and osseous; (2) from six to eight years, when they are mostly bony, periosteal and corneal; and (3) at puberty, when the corneal and nervous lesions are most likely to preponderate. In the latter two periods keen diagnostic study will often detect the heredosyphilitic even though the signs are not outstanding, and much can be done to arrest the progress of the disease through adequate treatment. But it is principally in the first age period, birth to six months, that the best hope of effecting a "cure" lies. A negative Wassermann reaction of the cord blood or of the mother's blood does not rule out the disease in the child. Unfortunately, also, a positive reaction of the cord blood or of the infant's own peripheral blood does not always mean syphilis either, because it has been several times convincingly shown that these early reactions frequently become spontaneously negative and that the infants have not been actually infected. However, Faber and Black (1936) showed that the quantitative, instead of the usual merely qualitative, method of performing the Wassermann test, could be used to considerable advantage, since with it the decline of the test toward zero can be detected by the end of the first week or even sooner; from a limited experience with this test, Ingraham *et al.* (1941) were also impressed with its ability to eliminate the nonsyphilitic patient. Roentgenologically, too, much assistance is to be had, for osteochondritis and periostitis, which the experienced man will confuse with no other lesion, appear in almost 100 per cent of cases within the first six months of life. Ingraham (1936) concluded, as the result of considerable study, that osteochondritis usually becomes roentgenologically manifest about five weeks after the fetus is infected, while periostitis requires approximately four months to develop. Serial roentgenographic study throughout all this period in order to detect the first appearance of the lesions is prohibitively expensive, but Ingraham was willing to make the prediction that a single roentgenogram made when the infant is six weeks old will detect almost every case; after further study, he (Ingraham *et al.*, 1941) seemed still of this opinion, adding that most of the conditions to be confused with syphilitic osteochondritis develop at a later period and even then show a type of early change usually demonstrable in congenital syphilis during the first month of life.

The treatment of late congenital syphilis is that of late or latent acquired syphilis and therefore requires no special consideration here save to say that the disease is often extremely resistant, especially when its chief manifestation is interstitial keratitis or some form of neurologic involvement; and, further, that the great rarity of syphilitic aortitis and valvular heart lesions in children and adolescents will lessen to a great extent the practitioner's fear of instituting "therapeutic paradox" (see under treatment of cardiovascular syphilis) in beginning the treatment of these young people; though it should be remarked that Hinrichsen's (1943) review of the literature caused her to con-

clude that congenital syphilis produces definite syphilitic interstitial and nodular myocarditis. The several special features of treatment in early congenital syphilis are presented below.

Standard "Conservative" Treatment.—In an authoritative statement for the United States Public Health Service in 1940, Cole *et al.* suggested the following scheme of timing the injections if the infant is not acutely ill.

Week.	Treatment.	Week.	Treatment.
1.....	Arsenical in one-third to one-half full dose.	29–40....	Bismuth—note overlap.
		41–48....	Arsenical.
2–10.....	Arsenical in full dose.	48–59....	Bismuth—note overlap.
10–19.....	Bismuth—note overlap.	60–65....	Arsenical.
20–29.....	Arsenical.	65–72....	Bismuth—note overlap.

If the infant is ill with early congenital syphilis it may do badly under this routine; in such cases it is considered advisable to begin the treatment with heavy metal and just attempt to prevent progression until the patient's general condition has improved. Howard (1939) considered it advisable to attempt some protection of the liver by injecting 50–100 cc. of 10 per cent dextrose solution intravenously preliminary to each arsenical injection in the first course.

The accomplishment of negative blood and spinal fluid tests, together with the absence of all signs and symptoms of the disease, are the aims of treatment, of course. Smith, at Johns Hopkins Hospital, permits probation if these criteria are satisfied after one year's treatment, but in blood Wassermann-fast cases he does not allow a rest period until the spinal fluid is found normal and treatment has continued through an arbitrary two years—persistence in these Wassermann-fast cases being due to his observation that relapse or progression is four times more frequent among them than among those in whom Wassermann reversal is secured. Beerman *et al.* (1942) concluded that the question of the transmission of syphilis to the next generation by those who themselves have acquired the disease *in utero* (third generation syphilis) is still debatable, though they reported 1 such probable case themselves.

Mapharsen, Neoarsphenamine and Bismuth Dosage.—The studies of Morgan (1938), Howles (1939) and Astrachan and Cornell (1943) indicated that mapharsen is superior to neoarsphenamine in congenital as it is in acquired syphilis. Cole *et al.* (1940) stated the appropriate dosage to be 0.5 to 1.0 mg. per kilogram body weight, but Astrachan and Cornell (1943) felt that 0.75 mg. per kilogram should not be exceeded in patients with any form of congenital syphilis. Stokes and Ingraham (1939) advised the following weekly dosage of neoarsphenamine and bismuth to be used in some such scheme as that shown in the chart above.

Neoarsphenamine: 10 to 15 mg./kg. (5 to 7.5 mg./lb.)

Bismuth: 2 to 4 mg./kg. (1 to 2 mg./lb.)

(The bismuth content of commercial preparations is stated on the package.)

In infants and young children jugular vein injection is easy of accomplishment: lay the child on the table with the head dependent and turned to one side;

crying brings out the jugular vein very promptly. Injection may also be made under the fascia of the scalp. Injection into the fontanel is very dangerous. The bismuth is given intramuscularly of course. Astrachan and Cornell (1943) stated that mapharsen can also be given intramuscularly in selected cases in which all attempts at intravenous therapy have failed.

Bismarsen.—This drug has the definite advantages of being given intramuscularly and of containing both arsenic and bismuth. Chambers and Koetter used it in 180 patients ranging in age from birth to fourteen years, the majority being more than three years old; Reilly's series comprised 170 children in about the same age range. The series of 147 cases of Beerman *et al.* (1942) were largely in the later stages equivalent to late latent acquired syphilis. It appears that active lesions heal somewhat more slowly under bismarsen than under the straight arsenicals though the ultimate result is quite as good. All observers are agreed, however, that improvement lags in interstitial keratitis. Stokes and Ingraham (1939) stated the dosage as 7 mg. per kilogram (3.5 mg. per pound). Injections are given once or twice weekly in courses of twenty with rest intervals of two weeks between courses.

Sulfarsphenamine.—This drug has certain advantages when substituted for mapharsen or neoarsphenamine in the arsenical-bismuth regime: (*a*) It is given intramuscularly and the discomfort due to injection is slight and the immediate reactions apparently few. (*b*) Its efficacy is apparently quite high. (*c*) It is easy to prepare by merely dissolving it in the ampule in 1 to 2 cc. (the less the better) of fresh sterile distilled water. (*d*) The solution is much more stable than that of neoarsphenamine though of course mapharsen is also stable in solution. There is however one outstanding objection to the drug: it is the most toxic of all the arsphenamines when given to adults, and though these serious reactions do not seem to occur with nearly so great frequency in infants and young children, the danger must always be held in mind. Stokes and Ingraham (1939) stated the dosage as 10 mg. per kilogram (approximately 5 mg. per pound).

Acetarsone (*Stovarsol*).—This arsenical compound has been much used in the treatment of congenital syphilis on the Continent for a number of years, but Whipple and Dunham (1938), who exhaustively and authoritatively reviewed this literature, stated that of about 40 reports only 4 could be found in which sufficient follow-up had been made to evaluate the drug. A few favorable American reports, employing relatively small series of cases, have appeared, but they seem to me to be overshadowed by the important unfavorable report of Pillsbury and Perlman (1939). The advantage that acetarsone can claim to have over the other arsenicals is that it can be given by mouth—but that is the sole advantage. It is cheaper than the other drugs, to be sure, but that will be a point in its favor only when it shall have been shown to be fully as satisfactory in completely "curing" congenital syphilis. The fact that acetarsone can be given into the hand of a child who visits the clinic or office alone and who is then told to take it home and insist that his mother administer the doses to him faithfully can only be considered an advantage by wishful thinkers. Furthermore, I cannot for the life of me understand why bismuth shall cease to be given once the use of this drug has begun. Is it that, having spared the child the arsenical half of his injections, we are under some sort of obligation to omit the bismuth portion too? Not all the Continental workers discarded in the beginning, nor have they yet discarded, the use of heavy metals between acetarsone courses.

The principal findings with regard to the drug by Pillsbury and Perlman, who studied its use in 187 patients at a children's clinic of the University of Pennsylvania Medical School, were the following: (*a*) It is an active antisyphilitic agent but its action is less rapid and less satisfactory than that of arsphenamine and bismuth preparations; (*b*) The incidence of all reactions, and the proportion of serious reactions, was very high; (*c*) Nephritic reactions occurring suddenly and insidiously are the greatest single drawback to the use of the drug; (*d*) Acetarsone is probably not administered as directed at home for the incidence of reactions among patients under controlled conditions in the hospital was four times that of the out-patients. Acetarsone is not Council-accepted (1944) for the treatment of syphilis. Hinrichsen (1942), of the U.S.P.H.S., concluded an exhaustive review of the literature of this subject by saying that unless the advocates of acetarsone therapy furnish proof based on well-controlled studies, their opinion that this drug is the ideal one for the treatment of infantile congenital syphilis still must be considered as opinion and not fact.

The high dosage latterly employed has already been revised, and nearly all users of the drug have gone back to the scheme of Bratusch-Marrain (1931), which follows:

One week	0.005 Gm. per Kg. daily	(1/12 grain per 2.2 lbs.)
One week	0.010 " " " "	($\frac{1}{6}$ " " 2.2 ")
One week	0.015 " " " "	($\frac{1}{4}$ " " 2.2 ")
Six weeks	0.020 " " " "	($\frac{1}{3}$ " " 2.2 ")

Length of course, nine weeks. Rest period between courses, six weeks.

Acetarsone is commercially available in tablets of several sizes. Yampolsky (1934) ordered all tablets to be made into powders; the patient then receives 21 powders weekly and is instructed to take 1 powder dissolved in water three times daily, one-half hour before eating; or the dose is given infants in the same way before feeding time.

Resistance of Interstitial Keratitis and Neurosyphilis.—Amelioration of interstitial keratitis usually lags woefully behind improvement in other respects. Still, Cole *et al.* (1937), reporting for the Cooperative Clinical Group, found that of patients treated with arsenicals and heavy metals within six months of the onset in the first eye, the involvement remains unilateral in 71 per cent, and that of all the patients with acute involvement six times as many untreated as treated individuals lost useful vision. In the Group's most recent report, Klauder and Van Doren (1941) advised that fever therapy be employed as soon as possible after the onset. Iodides are not to be used as they unfavorably influence final visual acuity, but the arsenicals and bismuth are to be administered according to the following schedule:

Weeks	
1 to 9	Arsenical, 10 weekly doses Bismuth (soluble), 8 doses, twice weekly, during first month
10 to 19	Bismuth, 10 weekly doses
20 to 29	Arsenical, 10 weekly doses
30 to 39	Bismuth, 10 weekly doses
40 to 44	Arsenical, 5 weekly doses
45 to 54	Bismuth, 10 weekly doses
55 to 59	Arsenical, 5 weekly doses
60 to 69	Bismuth, 10 weekly doses
70 to 73	Rest period
74 to 83	Bismuth, 10 weekly doses

An interesting new development in the treatment of this entity was Sydenstricker's (1941) report of the successful employment of riboflavin (see Index

for methods) in several cases; Corner (1944) also used riboflavin very successfully in 2 cases An ophthalmologist should see the case also, for the proper use of atropine and dionin locally may greatly contribute toward cure. Penicillin has also been used (see below).

The treatment of neurosyphilis in congenital syphilitics is the same as in syphilitics having the acquired form of the disease, but it is rarely successful. Indeed, progression often takes place in spite of the most vigorous use of drugs or fever therapy.

Intensive Therapy.—Levin *et al.* (1942) reported encouraging results from the employment of this method (described in detail in the section on the treatment of early syphilis) in 32 cases of infants and children with congenital syphilis. They experimented considerably with dosage, starting very conservatively at 1.6 mg. per pound body weight a day, but in the later patients giving as much as 3 mg. per pound body weight per day. The total dose for five days was calculated and divided as follows: On the first day of treatment 10 per cent of the total dose; on the second day 15 per cent of the total; and on the third, fourth and fifth days 25 per cent of the total. The amount of solution (5 per cent dextrose) used in infants was 30 to 60 cc. per pound of body weight a day, regulated to flow for a period of ten hours; for infants the amount of solution averaged between 300 cc. and 600 cc. a day, for older children a maximum of 1000 cc. was used.

Penicillin.—The most extensive employment of penicillin in the treatment of early infantile congenital syphilis is that reported by Platou *et al.* (1945), who pooled the experience with 69 infants gained by the university groups in Baltimore, Philadelphia, Galveston and New Orleans. Penicillin was given intramuscularly in saline solution every three hours in 60 injections over a seven and one-half day period, total dosage ranging from 16,000 to 32,000 Oxford units per kilogram of body weight. In general the immediate response was gratifying, cutaneous and mucous membrane lesions healing during or shortly after treatment, rhinitis in two weeks to two months. All darkfield positive lesions became negative within twenty-four hours after the start of therapy. Roentgenographic evidence of osteitis disappeared in two to six months, *i.e.*, at about the same rate expected after metal chemotherapy. Regression of hepatic, splenic and lymph node enlargement, though variable, was usually complete within three months. If abnormal spinal fluid findings were present initially, they returned to normal in all instances in from eight days to six months. Of the 69 infants, 39 were followed from four to twelve months; at the time of the report, 25 of these 39 were physically normal and showed doubtful or negative serologic tests (21 negative, 4 doubtful). In 9 of the 39, quantitative serologic titers were either stationary at moderately high levels or slowly declining, and these infants also were well. Serologic relapse occurred in 5 infants and clinical relapse in 2 of these 5, the serologic relapses occurring from three to six months after treatment, and the clinical relapse in each case at six months.

In 34 of these 69 infants reactions occurred during treatment, nearly all of them being mild and consisting of moderate fever beginning on the first or second day of treatment and seldom lasting longer than three days. One infant, forty-eight hours after treatment was begun, suddenly developed severe, nearly fatal, collapse. Three infants died during or soon after treatment (twenty-four hours, seven days and nine days after penicillin was started); all of these had active syphilitic lesions, were under two months of age and were

in poor general condition. Two other infants died five weeks and fourteen weeks after penicillin; whether the latter deaths were directly or indirectly due to penicillin or syphilis is not known.

Platou *et al.* felt that their findings indicated that the present total dose and time-dose relationship schedule of penicillin in early congenital syphilis is not entirely satisfactory. They therefore recommended that the total dose be raised to 40,000 Oxford units per kilogram of body weight, to be given in sixty intramuscular injections over a seven and one-half day period. They felt that persistent positivity of the blood serologic test alone is not yet to be considered an indication in itself for retreatment, but they thought that definite relapse—defined as either a persistently rising serologic titer or clinical evidence of progression of the disease—should be retreated at double the original dosage.

In late congenital syphilis, Stokes *et al.* (1944) felt that they obtained equivocal though at times dramatically favorable results with penicillin in interstitial keratitis. Of 14 cases there was 50 to 100 per cent improvement in 6, but 2 were made definitely worse.

Treatment of Late (Tertiary) Syphilis

Late syphilis of the liver calls for utmost caution in the therapeutic attack. A Herxheimer reaction in this organ may be fatal; or it has been considered that the patient may die in what Wile called the "therapeutic paradox." This latter is a state of affairs characterized by such rapid healing and cicatrization that the portal circulation is obstructed, with resultant ascites, or the bile ducts are occluded to such extent that the most severe jaundice develops. It is the usual practice therefore to aim at only a very leisurely promotion of reparative processes, employing continuous moderate to heavy use of the iodides with mercury courses superimposed upon this, about as follows: iodides, one week; iodides and mercury by mouth, two weeks; iodides and mercury inunctions, eight or nine weeks (occasionally giving a little mercury by intramuscular injection instead of the rubs, if this seems desirable); iodides alone for about four months. This cycle is repeated several times as dictated by progress in the case. If iodides are omitted for a while, it had better be during one of the periods when mercury is being given. The vast majority of patients are very much improved by such treatment as this. I think it should be noted however that in Hahn's (1943) treatment of 25 patients with hepatic syphilis at the Johns Hopkins Hospital, he found no evidence that hepatic damage due to syphilis predisposes to hepatic damage due to arsenicals; the "therapeutic paradox" was not observed in any of his cases, though he recommended that, because of the possible presence of lesions in the hilum, treatment should be initiated with *bismuth* (not mercury) and the iodides. He also felt that in the presence of ascites, arsenic therapy is probably contraindicated.

In practically none of the other usual types of late syphilis—gastric, and the rarer intestinal and rectal forms of gastro-intestinal syphilis; cutaneous and buccal manifestations of diverse nature; osseous and joint syphilis, etc.—need Herxheimer reaction or the "therapeutic paradox" be feared; treatment can therefore begin with the use of arsenic and can in general proceed much as in the treatment of acute syphilis. However, since most of these patients are in or approaching the years in which cardiovascular, neuro- and hepatic syphilis (all calling for a cautious attack) may be expected to occur, *every* diagnostic aid should be utilized to make sure that one or more of these entities is not

present as a complication. Some men favor beginning the treatment always with bismuth in these cases even though the patient seems to be clear of all syphilitic involvements save those relatively harmless ones which are presenting; progress is thus much slower of course. In some instances "mixed treatment" with mercury and iodides (see above) will alone be indicated; judgment must be exercised in each individual case. In the presence of a severe complicating nephritis only the iodides can be used with full safety. In late syphilis of the bones and joints, surgical and orthopedic aid may be highly desirable; indeed in Charcot joints accompanying tabes, the antisyphilitic attack is of itself impotent.

I have not as yet heard much of the employment of penicillin in late syphilis, though O'Leary and Herrell (1944) did report a striking result in a patient with a late cutaneous involvement.

Iodides in the Treatment of Syphilis

In numerous places throughout the discussion of syphilis I have referred to the use of iodides and wish here to set down briefly the more acceptable forms of iodide therapy.

Potassium Iodide.—*By Mouth.*—This is the cheaper salt and the one most frequently used. It is often stated that the sodium salt should be given the preference because of the depressing effect of the potassium ion on the heart, but Eggleston pointed out some years ago that potassium is eliminated from the human body with such rapidity that it is almost impossible to poison the heart by the administration of its salts by mouth; nevertheless, Steward and Smith (1941) demonstrated some very interesting electrocardiographic changes in patients taking potassium iodide, and one wonders whether the subject might profitably be reopened. Osborne's investigations at the Mayo Clinic suggested that the iodine given in the form of potassium iodide by mouth forms a sodium protein combination, while in the case of sodium iodide by mouth only traces of iodine enter into combination with the proteins—observations which may bear directly on the general clinical impression that, grain for grain, potassium iodide is more effective than sodium iodide.

As to dosage, I quote Barker and Sprunt: "Potassium iodide is usually prescribed in strong solution, an ounce of the salt being dissolved in an ounce of water, with the direction that the drug shall be greatly diluted as each dose is administered. Since an idiosyncrasy to the drug may be encountered, small doses are usually given at first, say 5 grains (*i.e.*, 5 drops of the solution—H.B.), three times a day, preferably given a half or three quarters of an hour after meals. Even when mild symptoms of iodism occur, they will usually disappear on increase of the dosage to 10 or 15 grains thrice daily. The dose has sometimes been increased, up to 300 grains (20 Gm.) or more a day. Large doses may cause gastric irritation, due to the salt action, symptoms that are quite distinct from those of iodism. This irritation may be obviated to some extent by administering the drug in milk or whey. Engman warns against the use of the excessive doses sometimes employed, especially in certain health resorts where many patients are treated. Fournier was also strongly opposed to what he called 'iodide debauches'; he seldom gave more than from 45 to 60 grains daily. When tolerance for the drug is established, the curative value apparently diminishes and the dose must therefore be increased."

The following prescription is probably as effective as any in disguising the drug; it will contain 15 grains (1 Gm.) in the teaspoonful dose:

℞	Potassium iodide	ʒj	30.0
	Compound syrup of sarsaparilla	ʒj	30.0
	Water to make	℥iv	120.0

Label: One or more teaspoonfuls in water as directed.

Garfield (1943) showed that satisfactory iodide effects can be obtained through the employment of enteric-coated pills containing 15 grains (1 Gm.) of potassium iodide. None of his 12 patients complained of gastric disturbances when taking these pills.

Sodium Iodide Intravenously.—Stokes feels that Osborne's work on the comparative penetrability of the nervous system by iodides when administered by mouth and by vein warrants the giving of sodium iodide intravenously in selected cases of neurosyphilis. He gives 30 to 150 grains (2–10 Gm.) in this way three to five times weekly, full doses by mouth being given meanwhile.

Iodism.—The symptoms are those of a "common cold" plus any one of a number of types of skin rashes, the latter often appearing some time after the former and occasionally, as in the astonishing case reported by Montgomery (1940), assuming a bizarre form. Some individuals never manifest these symptoms even on enormous doses, while others do so regularly when a certain dosage is reached. It is usually possible to disregard the iodism, but in some cases the drug must be omitted or greatly reduced for a time. Fever sometimes accompanies the other symptoms, but fever as the sole manifestation of iodism, as reported in 2 cases by Katzenstein (1938), must be a rare occurrence. The possibility of an iodide cachexia, in persons who have been taking the drug regularly for a very long time, must always be borne in mind. I think many of these cases pass unrecognized in some clinics.

Organic "Iodides."—More or less complex iodine compounds with proteins and fats, and one with methenamine (urotropin), have been introduced with claims that they are less irritating to the digestive tract than the metallic iodides and that they are less inclined to cause iodism. When given in the doses advised by the manufacturers they are usually distinctly less irritating to the stomach, but it is not quite certainly known whether these nonirritating doses are therapeutically as effective as the doses of metallic iodides that do cause irritation. Regarding the occurrence of iodism, it is doubtful if a susceptible individual will escape this symptom-complex if these newer preparations are used in doses comparable to those employed in treatment with the older simple iodides. The following are the Council-accepted (1944) preparations: iodalbin, supplied in 5-grain (0.3 Gm.) capsules; iodostarine, 4-grain (0.25 Gm.) tablets; lipoiodine, 5-grain (0.3 Gm.) tablets; riodine, 3-grain (0.2 Gm.) pearls; calcium iodobehenate (sajodin), 1- and 8-grain (0.06 and 0.5 Gm.) tablets; siomine, 1-, 2- and 5-grain (0.06, 0.12, 0.3 Gm.) capsules.

PROPHYLAXIS OF SYPHILIS

See under "Prophylaxis of Venereal Diseases."

TETANUS

(*Lockjaw*)

"Another receiv'd an insignificant wound to speak of (for it was not deep) a little below his neck behind from a sharp dart; which being taken out not long after, he was drawn and distorted backwards, as in the opisthotonus. His jaws were also fasten'd; and, if anything moist was put into his mouth, and he attempted to swallow it, it returned again thro' the nose. In other respects he grew worse immediately. The second day he dy'd."

—Hippocrates. Upon Epidemics. Book V. The Cases at Salamis—No. 15
(Translated by Clifton, London, 1734.)

Tetanus is an acute infectious disease caused by the infection of a wound with the spores of *Clostridium tetani*. The wound is usually an accidental one, though the organism has also contaminated burns and bedsores and suppurative otitis media. Tetanus neonatorum is becoming very rare now that the umbilical cord is properly cared for as a matter of routine, and tetanus following an abdominal operation is also nowadays a rare occurrence. Wainwright's (1926) compilation of 760 cases showed that 80 per cent were due to injuries on the street, on the farm, in homes, garden, stables, etc., and only 20 per cent to industrial accidents. That even our modernly constructed, smooth surface streets are still a potential source of danger was shown by the studies of Gilles (1937). Bush (1941) reported an interesting group of 5 cases (4 deaths) attributable to the introduction of a gauze pad into the cervix by an abortionist. The fact is now well established that the organism is harbored to a very considerable extent in the human intestinal tract as well as in that of the lower animals; Bauer and Meyer found spores of definitely toxic strains in 24.6 per cent of 487 specimens of feces from residents of California.

The interesting studies of Lahiri (1939), in India, indicated that there is no such thing as an environmentally acquired immunity to tetanus; *i.e.*, farmers and others exceptionally exposed do not apparently acquire specific antitoxic protection through subclinical infections. The tetanus organism grows best under the completely anaerobic conditions prevailing in deep wounds or those that have become scabbed over, and its growth is also aided by the concomitant presence of pus-producing organisms; the retention of a foreign body in a fresh wound also increases the chances of tetanus developing. However, tetanus occurs frequently from wounds so trivial that no attention is paid to them.

The almost universal belief that the toxin produced by the bacillus at the wound site reaches the central nervous system by traveling along the axis-cylinders of nerves or by way of the perineural lymphatics has been disturbed by the studies of Abel and his associates, more recently pursued particularly by Firor, which indicate that the only way the toxin can reach the central nervous system is by the blood vascular pathway; these workers have even suggested that the tetanus toxin in the cord is altered into or liberates a different agent which is transported to and has its lethal effect upon the vital centers. Of such disturbing heresies is our present great epoch compounded.

The prodromal symptoms, which it is important to recognize, are restlessness and hyperirritability, perhaps chilliness and headache with some general stiffness of the body, and, the most important symptom, a stiffness of the neck and difficulty in chewing and swallowing. A boardlike rigidity of the abdomen makes its appearance very early. The later, more typical, symptoms are frequent convulsions from which the patient does not at any time completely relax, the characteristic lockjaw (trismus), a sardonic facial expression, several degrees of fever with proportional leukocytosis, spinal fluid that is clear but

under increased pressure, and great pain from the severe muscular contractions; consciousness is often retained until the end, death usually occurring on the fourth or fifth day. It is said that if a patient survives the eighth day his chances of recovery are very good.

The incubation period of the disease is from three days to several weeks. Statistics, gathered from civil as well as military practice, show that most cases develop within from ten to fourteen days after the wound is suffered; it is axiomatic that the shorter the incubation period the higher the mortality. Since the prophylactic use of tetanus antitoxin has become more frequent, a local type of the disease with symptoms confined to the neighborhood of the wound is rather often seen. The mistaken tendency is to recognize this as a new entity, though there are records of numerous such cases before the introduction of antitoxin; sometimes these local tetanic foci precede by some time the signs of descending tetanus.

Mortality in tetanus is as high as 40, sometimes even 70 to 80 per cent. A few recent reports are showing an appreciably lower mortality than this under modern therapy, but it seems unwarranted to eliminate those who die within twenty-four hours of admission, as some authors are doing, in order to obtain the low figures; indeed, Dietrich (1940) felt that probably many of these early deaths are due to faulty therapy since they occur much sooner than they possibly could have done in untreated tetanus.

Vener and Bower (1940) reported a second attack of tetanus in the same patient and mentioned five other cases in the literature.

THERAPY

Sedatives.—Certainly the judicious employment of all available sedative measures is indicated in tetanus for it is our bounden duty to lessen as much as possible the terrific suffering of these patients. Spaeth (1940), in a careful analysis of results over a period of years in his hospital, reached the conclusion that even from the standpoint of reduction in mortality one is justified in placing great emphasis upon effective sedative therapy. He preferred avertin solution in the form of a retention enema, using 25 mg. per kilogram (12.5 mg. per pound) of body weight for the initial average dose to be followed at fifteen- to thirty-minute intervals with about half that dosage according to individual requirements. Sometimes initial dosage may have to be double that stated if the patient is having severe asphyxial spasms. No deleterious effects of avertin, other than slight transient rectal irritation, have been reported by any of the numerous observers, but Spaeth would prefer not to use it if there are renal or hepatic disorders. In one very severe case of tetanus neonatorum in an infant eight days old, Cole and Spooner (1935) used avertin in full adult dosage per pound of body weight and believed that this heroic measure saved the child's life; for twenty-five consecutive days the patient received never less than two instillations daily and for the first thirteen days often as many as four, five, or six.

Sodium amytal may be given by mouth, rectum, vein, or by intramuscular injection. Spaeth's routine initial dosage is 5 mg. per kilogram (2.5 mg. per pound) of body weight, with an upper limit of 240 mg. for children and 480 mg. for adults. One cannot too strongly stress that any barbiturate given intravenously must be given *exceedingly slowly;* my own feeling is that these drugs had best be given intramuscularly. Dietrich was well pleased with seconal in the 3 cases in which he tried it, using "knockout doses" of 3 to 4 grains (0.2 to

0.25 Gm.) every three to four hours in a child of five years. Phenobarbital sodium (luminal sodium) is also used; 3 to 6 grains (0.2 to 0.4 Gm.) is average adult dosage. Chloral hydrate is well absorbed from the rectum; 30 to 45 grains (2 to 3 Gm.) in olive oil or water every four hours is permissible dosage. Paraldehyde may also be given rectally: 1 to 6 drachms (4 to 24 cc.) in a few ounces of physiologic saline solution. This last drug was used in the majority of Yodh's (1937) series of 438 cases in India; 4 drachms (16 cc.) in 2 ounces (60 cc.) of physiologic saline solution by the drop method four-hourly, varied according to individual requirements. Morphine is valuable but must sometimes be given in doses so large as to be dangerous. As a matter of fact Firor's (1940) investigations indicated that the lethal agent in tetanus (the secondarily formed agent previously referred to) may act chiefly on the respiratory center; if this is proved to be a fact, of course caution in the use of these respiratory depressant drugs would be doubly enjoined, and this would apply also of course to magnesium sulfate (see below).

First used by Blake in a case of human tetanus in 1906, magnesium sulfate has off and on had its advocates but does not seem to have made a sure place for itself. If *complete* relaxation is sought with the drug it may be very dangerous, but used in moderate dosage it should not be. Calcium chloride will very specifically and immediately combat excessive respiratory depression caused by magnesium sulfate; inject 10 to 20 cc. of a 2.5 per cent solution of calcium chloride in physiologic saline intravenously (slowly). The following is a summary of the magnesium sulfate dosage which served Smith and Leighton as a working basis: *Subcutaneous:* 1 to 2 cc. of a 25 per cent solution for each 20 pounds of body weight, four times in twenty-four hours. Should be continued until disappearance of symptoms. *Intramuscular:* lightly anesthetize with ether and deposit intramuscularly 2 cc. of a 25 per cent solution for each 20 pounds of body weight; effect in less than half an hour and lasts two or three hours. *Intravenous:* most prompt but fleeting; effect may disappear in thirty minutes. Dose: 6 per cent solution, at rate of 2 to 3 cc. per minute until relaxation begins. *Intraspinal:* effect in less than half an hour and relief lasts twelve to thirty hours. Anesthetize with ether and inject 1 cc. of a 25 per cent solution for each 20 pounds; second dose, 0.8 cc. for each 20 pounds; only 0.5 cc. per 20 pounds in a child. Arnold and McDaniel (1939) employed all the above methods of administering magnesium sulfate except the intravenous, the latter being omitted because they thought it too dangerous and because injection by the other routes was very efficacious. Dastidar (1943), who used magnesium sulfate in 155 cases in India, preferred the intramuscular route because he felt the intravenous injection was dangerous, the subcutaneous injection painful and the intrathecal injection not practicable.

Antitetanic Serum.—There has been much skepticism in the profession regarding the value of antiserum in treatment, but recent writers seem to be favoring it again. Statistically, it has certainly not been possible to attest its worth for the reason that there are several variable factors: the severity of the case, the length of the antecedent incubation period, the general condition of the patient (*i.e.*, his ability to withstand attack of any sort), the amount of prophylactic serum that was used and the coincident employment of other therapeutic measures. Likewise, and for similar reasons, the matter of the preferred route of administration of the serum remains a controversial one. I shall summarize here the antitoxin method employed by Vener and Bower (1941), of Los Angeles, because it was based upon sufficient experience to give

it significance. After a preliminary injection of antitoxin around the wound site (see Local Treatment below) they inject 60,000 units of antitoxin intramuscularly. Then, as soon as sedation makes it possible, the occipital area is shaved and cisternal puncture is done, removing 10 cc. of fluid and slowly injecting by the gravity method 20,000 units of antitoxin. When the rise in temperature induced by the cisternal therapy has receded to about 102° F. (39° C.) rectal, 40,000 units of antitoxin are given intravenously; it is diluted in 300 to 500 cc. of saline and given by gravity, allowing at least an hour for completion of the injection. If there has been no systemic reaction to this first intravenous injection in four hours, a second of only 20,000 units but in the same amount of saline is given. Twelve hours after the second intravenous injection an intramuscular injection of 40,000 units is given; if reaction caused the omission of the second intravenous injection, this intramuscular injection is increased to 60,000 units. About 200,000 units have now been given within thirty to thirty-six hours; thereafter additional large doses are not given unless the patient relapses, but 1500 units are given subcutaneously at four- to five-day intervals for four doses to "keep the patient desensitized," and if future orthopedic or other surgical measures are to be taken these doses are continued until two weeks after this intervention.

Space would not permit citing the arguments of all those who disapprove the above type of therapy, but Spaeth (1940) probably summarized the position in stating his feeling that intraspinal and intracisternal therapy are to be avoided because of the excitement caused the patient, the technical difficulties in the presence of highly spastic states, and the danger of inducing sterile or septic meningitis in subjects already dangerously hyperexcitable. On the basis of titration studies performed by himself and by others earlier, Spaeth did not see the rationale of large and repeated dosage of serum. He proposed a single dose of 40,000 to 60,000 units to be given intramuscularly or intravenously, the larger dose and the intravenous route for those admitted during the first four or five days of the disease. Dietrich (1940) said that, in children at least, both the intrathecal and intravenous routes are very dangerous and that he prefers to run the risk of a slower effect by giving the drug intramuscularly; he said he likes to supply a continuous but moderate amount of antitoxin to neutralize any new toxin liberated and that the administration of 10,000 to 20,000 units daily for two to four days is adequate for this purpose.

Reactions.—Vener and Bower said that if a patient is especially sensitive to horse serum or subject to some type of allergic attack, or previously has received prophylactic antitoxin followed by a serum reaction, the intravenous and intrathecal procedures should be omitted and instead two intramuscular injections of 100,000 units each should be given with an interval of twelve to eighteen hours. Spaeth routinely injects adrenalin (epinephrine) and atropine before injecting serum, even intramuscularly, in all patients whether known to be sensitive or not, the serum injection to be made not earlier than thirty minutes after this preparatory injection. His dosage follows:

	6 mo.	*2 years*	*5 years*	*Adult*
Adrenalin (1:1000)	3 minims (0.18 cc.)	4 minims (0.25 cc.)	5 minims (0.31 cc.)	8 minims (0.49 cc.)
Atropine sulfate	1/500 grain (0.12 mg.)	1/250 grain (0.24 mg.)	1/200 grain (0.3 mg.)	1/100 grain (0.6 mg.)

Serum sickness (see Index) is usually reported to occur in eight to ten days in half or more of those receiving the antitoxin; in Vener and Bower's series of

100 cases there was an incidence of only 39 per cent, which they attribute to the refinements in serum manufacture in recent times. A bovine serum has been available for some years but does not seem to be much employed. In a markedly sensitive individual, Schaeffer and Myers (1941) have successfully employed a horse antitoxin "despeciated" by a method devised by Coghill *et al.* Any type of tetanus antitoxin must be warmed to body temperature before injection.

Toxic neuritis of various nerves, including the auditory, has been reported a few times after the use of tetanus antitoxin.

Local Treatment.—Miller lays down the principles of local treatment as follows: "1. Sterilization of the part. 2. Thorough opening of the wound in its whole breadth and depth. 3. Débridement—complete excision of every scrap of dead or infected tissue. 4. Sterilization of the wound. 5. Measures to keep it open. It must not be 'packed,' though gauze, preferably soaked in hydrogen peroxide, may be laid gently in it. It must not be tightly bandaged. Anything tending to close the wound, and shut out the air, must be avoided. The dressing should be renewed very frequently."

In writing of the sterilization of the wound, one should perhaps specifically mention the tincture of iodine, for it not only tends to prevent secondary infection, but seems to have a local specific effect against the toxin. MacConkey and Silva have shown that mixing iodine with toxin definitely lessens the strength of the toxin. There are no data known to me to show whether or not this property is common to all the penetrating disinfectants, such, for instance, as the dyes which have become so popular for local use.

In regard to the matter of thorough incision and excision of the wound, it is of interest to note that Sir David Bruce stated that surgeons were slow to realize the importance of this method during War I, but that, had the war lasted longer, tetanus would probably have been extinguished. More recent writers urge not only débridement of the open wound but that all apparently healed wounds be opened widely and foreign bodies sought and removed. It is also considered advisable to give the first dose of antitoxin as soon as the patient is anesthetized and before beginning any surgical manipulations which may spread the toxin. Vener and Bower (1941) preceded surgical procedures forty-five to sixty minutes by injecting 20,000 units of antitoxin completely around the lesion and then kept the operations within this encircled field. Subsequently they treated the area as though infected, using hot compresses of potassium permanganate solution.

Spaeth (1940) disagreed with the above position, feeling that under no circumstances should one resort to amputation, excision, or drainage for the sole purpose of removing foci at which toxin is being elaborated—at least he stressed that sedation and antitoxin are of primary importance and that thereafter the handling of the local lesion should simply be in accordance with the principles of surgery in the absence of tetanus. Unfortunately, in children and in adults who environmentally sustain trivial wounds with great frequency, the inciting wound is often not identifiable and thus local measures cannot be applied even though they might have been desirable.

All surgeons are in agreement that the wound should under no circumstances be cauterized, for the resulting area of necrosis is altogether to the taste of the tetanus organism.

Penicillin.—Buxton and Kurman (1945) reported 2 cases in which recovery followed the employment of penicillin in addition to the antiserum; in one of

the cases sulfadiazine was also used. Of course it will require much more experience than this to prove the effectiveness of penicillin in human tetanus, though the agent is known to be effective against *C. tetani* under experimental conditions.

Miscellaneous Drugs.—*Curare*, the South American arrow poison which paralyzes voluntary muscular movement by blocking the passage of impulses from the motor nerves to muscles, has been introduced into medicine and abandoned again on several occasions. The latest reports I have seen were those of Cole (1934), Mitchell (1935) and West (1936), who either employed the crude drug or its chief active principle, curarine. There is no very good evidence, however, that anything of much practical value has come out of these studies as yet. The experiments of Perlstein and Weinglass (1944), employing dogs, showed that prolonged curarization such as would be necessary in the treatment of tetanus has a lethal effect in animals in spite of artificial maintenance of respiration. *Phenol intraspinally* was knocking about for a good many years before Swansa reported some apparently good results with it in a small series of cases, in 1931. Since then Thompson and Friedman (1941) failed to find any rationale for the employment of this agent in their careful experimental studies, and since the proportion of serious reactions was high in Swansa's cases I feel that description of the methods of employment may be well omitted from this edition of the book. There came out of France, in 1938, a report of the successful employment of *alcohol intravenously* (10 to 40 cc. daily of a 33 per cent solution in 30 per cent dextrose), but I have heard nothing further of this. Vener and Bower (1941) gave *methenamine* (*urotropin*) *intravenously* in doses of 15 grains (1 Gm.) with a list of four rationalizing reasons, none of them impressive.

General Nursing and Dietary Care.—Upon the whole the advantage of keeping the room darkened and as quiet as possible has not been stressed in the literature as much as it might have been; reflex spasms can be considerably reduced in number by these measures alone. It seems hardly necessary to mention that someone in attendance should watch the patient unobtrusively at all times so that artificial respiration may be quickly applied as soon as needed. A liquid diet (see Index) is preferred because of the greater ease with which it may be swallowed, but in some instances when sedative measures have not sufficiently relaxed the jaw to permit the administration of food by mouth, nasal duodenal tube feeding (see Index) will have to be resorted to. Rectal feeding (see Index) is less satisfactory for the reason that the patient in tetanus needs more food than can usually be given by that route; furthermore, sedatives are likely being given rectally. The advantages of intravenous dextrose administration should not be overlooked. Constipation is often present and requires the use of enemas in preference to cathartics. Bladder distention should be relieved by catheterization before it increases the patient's restlessness. There is no contraindication to warm sponge bathing unless it aggravates the spasmodic condition.

Pneumonia is the great enemy, to be forestalled if possible by keeping the patient off his back and shifting him from side to side frequently, also by attempting to maintain oral hygiene through gentle cleansing of mouth and nasal passages and at times the use of a suction apparatus to take up the secretions which cannot be easily swallowed. I should think that sulfadiazine in prophylactic daily dosage of 15 grains (1 Gm.) would be definitely indicated. Vener and Bower (1941) advocated shrinking the nasal mucous membranes

at frequent intervals in the attempt to avoid sinusitis; moderate elevation of the foot of the bed may also be helpful.

PROPHYLAXIS

This subject has nowadays to be considered under several separate heads: passive immunization with antitoxin at the time of injury, active immunization with toxoid before the receipt of injury and the combination of the two methods.

Passive Immunization with Antitoxin.—The injection of antitoxin at the time of receipt of a wound thought likely to eventuate in tetanus is not an infallibly protective measure but its great efficacy is now so universally recognized that I shall not labor to prove the point here. The objectionable features of this type of prophylaxis, however, are several: (*a*) The protection conferred lasts only for ten to fourteen days, and hence if the wound has not healed in that time or is a lacerated one containing dead spaces, a foreign body, or necrotic tissue, the dose has to be repeated at intervals of a week to ten days. (*b*) Subsequent injuries, or reactivation of a latent infection, require further antitoxin injections. (*c*) The reactions characteristic of its therapeutic use are also to be expected when it is used prophylactically; of Newell and McVea's (1940) 500 patients, 59 experienced a reaction of some sort, the reaction being a general systemic one in 22 instances. (*d*) For best results the serum should be kept in a refrigerator.

The dosage employed is almost universally 1500 units, given intramuscularly, but this is well increased to 5000 units if the injury is of the suspicious nature above described; Spaeth (1940) said that in the event one or more days have elapsed after the receipt of such a wound, the minimum initial dose should be 20,000 units. Teare (1944) said that it is the practice in most London teaching hospitals to give prophylactic injections of antitetanus serum on the eighth and fifteenth days after the initial dose to guard against the onset of tetanus after a long incubation period, and he felt that this practice should be more widely known.

Active Immunization with Toxoid.—How many millions of persons—and animals, for tetanus has always taken a high toll among horses—have been injected with toxoid since the method was introduced by Ramon and his associates is not accurately known, but the number is enormous and reactions, which are nearly always mild, are exceedingly rare. Such immunization should be employed by farmers and certain industrial workers and by all others whose occupations or avocations make them especially liable to tetanus infection. The toxoid should also be administered routinely to all children. Long (1944) reported that in the American Army, every member of which is protected against tetanus by the use of toxoid, only 9 cases of tetanus had been reported over a period of almost two and one-half years; none of these cases followed battle injury and only 2 occurred in individuals who had completed their initial series of injections.

The method of immunization employed in the Army is the administration of plain or fluid tetanus toxoid in a series of three subcutaneous injections of 1 cc. each at intervals of three weeks. Under ordinary circumstances a single stimulating dose of 1 cc. is administered at the end of the first year after the initial series, another 1 cc. dose is administered prior to departure for a theater of operations unless such departure is within the six months' period subsequent to the administration of a previous dose, and an emergency "boosting" dose is

given upon the occurrence of wounds or severe burns on the battlefield or at the time of secondary operations or manipulations of old wounds, or at any other time when danger from tetanus is considered to be a possibility.

Since a few cases of general reaction which seem to be related to the allergic constitution of the patient have been recorded, Cooke *et al.* (1940) warned that preliminary skin testing with the toxoid should always precede the administration of the second dose, but as these authors are specialists in allergy it seemed to me at the time that one might perhaps consider them a bit unduly alarmed. Gallagher *et al.* (1942) compared the unfavorable reactions occurring in 430 adolescent boys with no history of allergy and 75 with a history of allergy, finding a possibly slightly higher incidence of such minor reactions as occurred in the allergic group. It was also suggested in Circular Letter No. 110 from the Surgeon General's Office early in War II that tetanus toxoid be given in divided doses to persons with a positive skin test to it. All of this seems to me ultraconservative but perhaps that is as it should be.

Diphtheria-tetanus Toxoids Combined.—It is practically routine pediatric practice in the United States to immunize infants and children with the combined toxoids of diphtheria and tetanus which have been amply shown each to exert their antigenic properties uninfluenced by the other. Bigler and Werner (1941) thoroughly studied the subject and found this practice has everything in its favor and apparently nothing against it. As a result of their study of the antitoxin titers in 100 children, the majority being immunized when they were just under one year of age, Yeazell and Deamer (1942) concluded that a basic immunization with three subcutaneous injections of 1 cc. of a precipitated combined diphtheria and tetanus toxoid constitutes adequate protection against tetanus for the majority of persons if a stimulating dose of tetanus toxoid is given every two to three years and on receipt of injury. The usual interval of time between the administration of the basic doses is three weeks, but Peshkin's (1944) study indicated that a lengthening of this interval might possibly be advisable.

Combined Diphtheria, Tetanus and Whooping Cough Immunization.—Hamilton and Knouf (1944) reported the use of a mixture of the toxoids of diphtheria and tetanus, to which was added pertussis vaccine, in the immunization of 64 children against all three diseases. All of the children were between one and two years of age and were given 0.5 cc., 1 cc. and 1 cc. doses subcutaneously in the deltoid region at about four-week intervals. Blood was drawn for laboratory testing three months after the last injection, and upon the basis of the laboratory findings at least it seemed that the immunity achieved compared favorably with that expected when each of the antigens is given separately. Reactions seem to have been practically non-existent since it required questioning of the mothers to develop the fact that a few children had been fussy and seemed to have a little tenderness at the site of the injection. Further study of this method of immunization will be watched with much interest.

Active-passive Immunization.—When an individual, not previously immunized, receives a protective dose of tetanus antitoxin at the time of an injury, the question often arises whether this is not also a good time to begin toxoid injections; in short, may not the total immunity be greater if one engrafts an active immunity, through toxoid injections, upon the passive immunity obtained by use of the antitoxin? Ramon (1940), who certainly should be listened to, answered in the affirmative, but there are numerous evidences,

notably in the work of Frey and Schmid (1939), Otten and Hennemann (1939) and Cooke and Jones (1943) that workers in this field are not satisfied with this answer. As things stand, I should say that one should not undertake such a procedure.

TONSILLITIS

Acute tonsillitis is characterized by a rather sudden onset with aching pains throughout the body, very sore throat, high fever and rapid pulse, and considerable prostration. Susceptible individuals often have an annual attack some time during the inclement months; the usual duration is three to eight days. The possibility of diphtheria is usually easily ruled out by a careful examination of the throat. A streptococcus is the organism most frequently cultured from these throats.

THERAPY

Tonsillitis *per se* is rarely, perhaps never, fatal, but as an attack often ushers in a bout of rheumatic fever, and as there are not infrequently complications, the disease merits serious attention. Perhaps the sulfonamides are used more often in tonsillitis than in any other entity. Rhoads and Afremow (1940) treated 67 nurses at the Cook County and Evanston Hospitals in Chicago, 31 receiving sulfanilamide and 36 not being given the drug; no beneficial effects were observed but there were reactions in a few instances which gave cause for genuine concern. However, Freis (1944) performed a well-controlled study on 405 soldiers ill with tonsillitis during War II and observed reductions in duration of the malady and in incidence of complications which were slight but considered to be of statistical significance—the drug used by Freis was sulfadiazine given in dosage of 2 grains (125 mg.) by mouth four times daily. Plummer *et al.* (1945) treated 28 patients who had positive hemolytic streptococcus cultures with penicillin, giving the agent in a dosage of 15,000 units every four hours over periods varying from twenty-four hours to six days. The cultures became negative within twenty-four hours after the institution of treatment and remained so during the course of therapy, but hemolytic streptococci tended to return gradually to the nasopharynx when treatment was discontinued. In 19 of the patients who were given penicillin for sixty-four hours or more symptomatic relief commenced in eight to twelve hours after the beginning of therapy and was complete in twenty-four to thirty-six hours. However, clinical relapse occurred in 4 of the 9 patients treated for less than four days though it did not occur in any of the 10 treated for six days. One patient treated with penicillin for six days subsequently developed acute hemolytic streptococcic sinusitis and pneumonia.

For the general principles of "fever" treatment, the reader is referred to the article on the Common Cold. The vexed question of tonsillectomy is discussed in the article on Rheumatic Fever.

TOXOPLASMOSIS

Infection of birds and mammals, particularly rodents, with the intracellular protozoan parasite toxoplasma is world-wide in distribution, but it was not until the appearance of the report of Wolf, Cowen and Paige, in 1939, that we

became aware of such infections in man. Since this first report cases have been found in Europe and South America as well as in widely scattered areas throughout the United States. It is suspected that the human infections are derived from animals but nothing is known of the mode of transmission. The fact that serum of experimental animals and human beings who have survived infection with toxoplasma shows protective power was used by Sabin (1939) in the development of a test by which it has been possible both to identify toxoplasma and to demonstrate the presence of infection in patients and in apparently normal individuals. Since many of the cases of the infantile form of toxoplasmosis have apparently been infected *in utero* of mothers whose serum yielded positive protection tests, it is very likely that in time there will be divulged a large reservoir of inapparent infections in man and that the possibility will have to be considered of insect transmission from man to man as well as from the lower animals to man.

Most of our knowledge of the infantile form of toxoplasmosis is derived from the report of Cowen, Wolf and Paige (1942), who reviewed 11 cases of their own and 4 from the literature. In these cases the onset was usually within the first four days of life and nearly always within the first few weeks, and the outstanding evidences of organic brain damage were convulsions, muscular twitching or tremor, strabismus, occasionally retraction of the head, altered reflexes, nystagmus, disturbed ocular movements, marked variations in body temperature, and at a later stage retardation of mental and speech development. Hydrocephalus, caused by closure of the aqueduct of Sylvius or the foramen of Monro, was usually clinically evident or roentgenologically demonstrable. Nodules of calcification scattered through the cortex, basal ganglia and thalami were demonstrated by x-ray in 9 cases examined and found at autopsy in 3 others. Areas of chorioretinitis were nearly always found and there was often well-marked primary optic atrophy and diminution of visual acuity. Microphthalmus was a common finding. Fever was usually absent or only very slight in the early stages. In the 4 cases in which cerebrospinal fluid was examined it was found to be usually xanthochromic and having an increased protein content and in 4 of the 6 cases there was a pleocytosis. In 2 cases there was a maculopapular eruption and in 3 enlargement of the liver and spleen, jaundice being present in 2 of these 3 cases. Most of these patients died within a few months and at autopsy there was found massive destruction of brain tissue as a result of scattered focal lesions marked by inflammation, necrosis and a marked tendency to early calcification. Toxoplasmata were present in the brain tissues and in the cerebrospinal fluid, but it seems that they may also be present in other tissues without causing reaction.

In the report of Cowen *et al.* there were included also 6 cases in older children who had probably survived an infection in infancy. The common symptoms in these children were healed areas of central chorioretinitis, poor vision, hydrocephalus, convulsions, motor disturbances and some degree of mental deficiency. In 9 out of 10 cases in older children and adults who showed a similar type of chorioretinitis without other clinical evidences of infection, and in 7 children with atypical encephalopathies without retinal lesions, Sabin and Reichman (1942) obtained positive protection tests. Crothers (1943) also reported 9 cases in older children, all of the 8 cases tested giving positive protection tests.

Very little is known about the active form of the disease in adults. Pinkerton and Henderson (1941) reported 2 cases in which fever, prostration and a macu-

lopapular rash followed upon a brief prodromal period of weakness and malaise, the rash being generalized except for the scalp, palms and soles. In one of the cases there were signs and symptoms of atypical pneumonia and the findings at autopsy in both cases were those of interstitial pneumonia, focal necroses in the spleen and liver, minute focal lesions in the myocardium and also focal lesions in the brain of the one case examined. Toxoplasmata were found in the lesions and in one case they were demonstrated in the blood ante mortem and in the lesions by animal inoculation. Guimarães (1944) reported the case of a youth of eighteen whose disease lasted twenty-seven days and was characterized by high fever, paresis of the lower limbs, nuchal rigidity, dysphasia and monocytosis. Postmortem examination revealed encephalitis, pericarditis, nephritis and a meningo-encephalomyelitis with extensive inflammatory areas. Toxoplasmata were found in the lesions.

THERAPY

Sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine have been given therapeutic trial in experimental animal infections by Sabin and Warren (1942) and Weinman and Berne (1944). Both sulfapyridine and sulfathiazole were found effective if given very early in the course of the infection, sulfapyradine being the more effective of the two. Trial of these drugs in human cases in which very early diagnosis has been made would certainly seem justified. Neither atabrine nor quinine has been found to have any value in the experimental infections.

TRYPANOSOMIASIS

(*Sleeping Sickness*)

There are five major infectious diseases whose entire handling has been taken over quite properly by public health authorities or other specialists of great experience. These five are Asiatic cholera, leprosy, plague, trypanosomiasis and yellow fever; and since they do not nowadays raise problems in treatment for the general practitioner, I shall no longer allot space to a consideration of them in this book.

TUBERCULOSIS

Nowadays we classify systemic infections with *Mycobacterium tuberculosis* into two distinctly different sorts according to whether the body is reacting to the first or the second assault of the organism. The lesion of first-infection tuberculosis is usually microscopic in size and only very occasionally gives rise to signs which may be detected roentgenologically in the lung or regional lymph nodes. Being also practically always asymptomatic it is usually not clinically diagnosed, but the positive tuberculin test indicates its presence. Typical disposition of the lesion, apparently accomplished through the natural resistance of the body, consists in deposition of lime salts within it until com-

plete calcification has taken place. Within the core, however, tubercle bacilli may remain alive and virulent throughout the remainder of the patient's life. First-infection tuberculosis is always the same, whether it took place last month or fifty years ago; the infant, youth and adult all react in the same way to the bacillus the first time it attacks except that in the adult, according to Long (1943), calcification does not take place as readily as in the child and that radiologically visible lesions of first infection in adults may progress gravely unless they are treated by rest and other means, whereas in children, at least in white children, such lesions ordinarily regress while the child pursues its normal life. A positive tuberculin reaction merely tells us that a primary implantation of the tubercle bacillus has occurred in the patient, but it does not indicate to us at what time in his life this implantation took place, nor does it tell us whether the individual has the disease tuberculosis. Most of us who must sadly confess to being middle-aged or worse are positive tuberculin reactors for the reason that in the years of our infancy and childhood little was being done to protect individuals from contamination with tubercle bacilli. Likewise in congested areas where little preventive work is going on today, the young are still almost 100 per cent tuberculin-positive, but such high incidence of first infections no longer prevails widely throughout enlightened communities. The following are the figures on 97,548 tuberculin tests performed in my own state by the Wisconsin Antituberculosis Association through 1940 (kindly made available to me by Dr. Florence MacInnis and Mr. Harold Holand): birth to five years, 7.7 per cent; five to nine years, 5.0 per cent; ten to fourteen years, 9.3 per cent; fifteen to nineteen years, 13.9 per cent; twenty to twenty-four years, 23.6 per cent; twenty-five to twenty-nine years, 37.6 per cent; thirty to thirty-four years, 47.6 per cent; thirty-five to thirty-nine years, 59.3 per cent; forty to forty-four years, 58.8 per cent; forty-five to forty-nine years, 70.5 per cent; fifty to fifty-four years, 63.2 per cent; fifty-five to fifty-nine years, 74.1 per cent; sixty to sixty-four years, 66.7 per cent; sixty-five to sixty-nine years, 61.1 per cent; seventy years and over, 40.0 per cent. These figures give the picture in a progressive agricultural-industrial region with a population of average stability and not top-heavy in the higher age groups. In a study of the student body at the University of Wisconsin, Stiehm (1939) found that the incidence of positive reactors was lowest in those coming from the North Central (25.7 per cent) and the Mountain states (26.3 per cent), and highest in those from the Desert states (84.6 per cent), the Eastern states (42.8 per cent), the Southern states (42.4 per cent), and foreign countries (67.6 per cent).

This is, then, first-infection tuberculosis, a condition that in itself is almost invariably harmless (except in certain adults as pointed out above) but that is nevertheless of the utmost importance to the individual in whom it exists, since it makes him very vulnerable to the attack of the organisms the second time they assail him. The reason for this vulnerability is that during the course of the first infection, when the body was successfully protecting itself by throwing a wall of calcification around the invaders, the tissues became sensitized to the tuberculoprotein and a state of allergy was established quite comparable to that obtaining in the sufferer from ragweed pollinosis. In the latter, subsequent inhalation of sufficient of the pollen touches off his typical hay fever attack; in the individual in whom the positive tuberculin reaction tells us there is a focus of first-infection allergy-inducing tuberculosis, subsequent infection with sufficient numbers of tubercle bacilli containing the specific protein causes

the appearance of lesions of such destructive nature that they can be arrested or entirely healed only with the greatest difficulty. It is this reinfection type of the disease with its well known signs and symptoms which is commonly designated "tuberculosis."

The source of the second infection may be exogenous (from bacilli distributed by some other individual in an infectious stage), or endogenous (the individual's own organisms having escaped into the blood stream, a bronchus, the subarachnoid space, or some other part of the body, through a defect in the walls which were built up around them during the asymptomatic conquering of the first infection). Endogenous reinfection is fortunately rare and usually occurs in infants or young children within three months from the time of the first infection; the most frequent clinical forms are the deadly tuberculous pneumonia, diffuse tuberculous meningitis and miliary tuberculosis. Exogenous reinfections are the much more common, chronic and amenable forms: pulmonary tuberculosis, bone and joint tuberculosis, peritoneal tuberculosis, skin tuberculosis, genito-urinary tuberculosis, and so on.

Pulmonary tuberculosis, the most common of all the types of reinfection tuberculosis, is of infrequent occurrence under the age of ten or eleven years, but increases rapidly in incidence after that period. Therefore any child having a positive tuberculin reaction at the age of ten should be very carefully observed thereafter for the early signs or symptoms of reinfection. At Lymanhurst Health Center, in Minnesota, Ch'in *et al.* (1939) made a ten-year follow-up study of 1218 children seven years of age at the beginning, 446 positive reactors without clinical lesions and 772 negative reactors. At the end of the study there were 9 cases of tuberculosis in the original positive reactors to 1 in the negative reactors and the mortality ratio between the positive and negative reactors was 38 to 1. The annual or semi-annual roentgenogram is to be highly recommended since it will often detect a pulmonary lesion many months before other evidences of its presence appear. For those who present significant shadows Myers' (1939) recommendations were that the complete study then indicated include examination of the sputum and gastric contents for acid-fast bacilli, periodic red cell sedimentation tests, observation for symptoms, examination for abnormal physical signs and frequent roentgen examinations to determine whether the shadow persists or changes in size. Foley and Andosca (1943) felt that the importance of gastric lavage for the detection of tubercle bacilli cannot be overestimated since 29.2 per cent of their 639 patients with negative sputum were found to be positive by gastric lavage; the statistical findings of Feld (1944) were similar. On the basis of a study of the erythrocyte sedimentation rate of 2640 tuberculous patients, Banyai and Cadden (1943) felt that the clinical value of the erythrocyte sedimentation test had come to be greatly overestimated in tuberculosis work and that it should not be used as an independent index in the management of patients.

In the code of Hammurabi, written at least as long ago as 2000 B.C., there are indications of a knowledge of tuberculosis. The classical Greek writers described its clinical features and were aware of its contagiousness, but the latter point was not proved scientifically until Villemin devised his great experiments in 1865. The other outstanding advances of the nineteenth century were Laennec's remarkable studies with his new stethoscope, Louis' correlation of symptoms and pathology, Trudeau's pioneering in the sanatorium management of patients, and finally, in 1882, Koch's discovery of the causative organism. In the western world the tuberculosis death rate has been declining

very markedly in recent times except for a temporary setback due to the abnormal conditions obtaining during War II. Pronounced and widespread improvement in the economic status of the masses, combined most likely with other factors which we do not understand, have been at work to lower the rate, but undoubtedly our own deliberate efforts have greatly contributed to bring about the result through: (*a*) slaughter of cattle that are positive tuberculin reactors; (*b*) pasteurization of milk; (*c*) isolation of individuals with open and infective lesions of pulmonary tuberculosis; (*d*) education of the public to aid in preventing spread of bacilli; (*e*) modern collapse therapy which checks dissemination of organisms; (*f*) persistent efforts to detect and isolate unsuspected infective cases. In the United States the practical eradication of bovine tuberculosis (every county in the country now has less than 0.5 per cent of infected cattle) was accomplished only through the slaughtering of 4,000,000 tuberculous animals. Our death rate among whites was said by Dublin (1941) to be the lowest in the world, but in our 13,000,000 Negroes there is still a tremendous reservoir of the disease. Dublin said that their tuberculosis status has not risen above that of the white population in 1910. The average death rate from the disease in Negroes is three and one-half times that of the whites—but this is only the average, for in many cities the figure is even higher (nearly five times the white rate here in Milwaukee). The fact that this disproportion is chiefly a reflection of the relative poverty of the Negroes only intensifies the disgrace. Epidemiologists say there should be 2 hospital beds per death; in the North and West there are 2.1, in the South 0.7. But the South is stirring, and doubtless there will be a vast improvement in the situation in the relatively near future. Ringer's (1940) conviction that Negro doctors and nurses are needed to work among their own people in the South is certainly in line with the experience of some communities in which Negroes live in the North.

The death rate from tuberculosis is substantially higher in males than in females everywhere. Jews are relatively insusceptible to the disease. Throughout the Orient and in some portions of the tropics tuberculosis is still fatally rampant in all age groups, and even in the Occidental and enlightened lands it is still foremost as a cause of death in adolescence and early adulthood. In these latter portions of the world its supremacy is overthrown by heart disease, nephritis, cerebral hemorrhage and cancer only after the fortieth year of life. Said Opie (1935): "Since death with increasing age must be regarded as inevitable, tuberculosis may still be regarded as our foremost public health problem."

THERAPY

Sanatorium Regimen.—"When we speak of the treatment of tuberculosis, especially pulmonary tuberculosis, we envisage sanatorium regimen, which is the basis of all treatment of the disease; practically every other form of therapy is being applied by its practitioners to patients who are undergoing institutional care or some analogous substitute." Thus Krause in 1926, and I wish the reader to understand that in what follows I am always presupposing "sanatorium regimen," whether it be practiced in the home or in the hospital. Absolute rest in bed during the febrile periods, perhaps to be carried to the point of complete postural rest at times, as advocated by Webb and his associates, and to be followed later by carefully graduated exercises; a sufficient dietary composed of nutritious and palatable foods; the treatment to be carried out as nearly as possible in the open air; such changes of climate and general

environment as afford the best opportunity of "building" resistance; and skilled medical supervision at all times—these are the important factors. I believe it is the consensus that in any case the minimum amount of bed rest should be three months; in some cases this will have to be extended to six months or a year or even longer.

Collapse Therapy.—Artificial pneumothorax and the several surgical procedures for inducing partial or complete collapse of the diseased lung have rapidly advanced into the forefront of the battle against tuberculosis. Drolet's (1943) exhaustive statistical analysis showed that mortality apparently has not declined with an increased use of collapse therapy, though when Davidson (1943) got through analyzing this analysis it appeared that the findings did not mean what they had seemed to mean. It would seem to be undoubted fact that collapse therapy restores many patients to health and economic independence, but I am unable to present to the reader a clear-cut statement of the indications and contraindications for the employment of these measures since those able to speak authoritatively are still in disagreement. This much is certain, that no one, not even any of the most ardent champions of collapse therapy, is today advocating the use of these measures indiscriminately in all forms of pulmonary tuberculosis. Mayer (1942) stated the authoritative opinion that collapse therapy should be resorted to only after bed rest has been given adequate clinical trial, or when the character of the lesion is such that rest alone offers no hope of success, or when collapse is required for the safety of the patient as in instances of hemorrhage or imminent danger of spread of the disease. Ringer (1940) said that collapse therapy was employed as follows in three well-known institutions: Hudson County, New Jersey, Sanatorium, 44 per cent; Sea View Hospital, Staten Island, N. Y., 40 per cent; Chicago Municipal Hospital, 46.6 per cent. The average in 26 institutions in the South, of which he inquired, was 47.1 per cent. It seems to me that, where not forced into the frequent employment of artificial pneumothorax as an expedient procedure when the number of available beds is severely limited, the best course for any practitioner is to be guided in his practice by those in his community who have had most experience with these measures—and to see to it always that the one he follows is a conservative fellow!

Heliotherapy.—In his special article under the auspices of the American Medical Association Council on Physical Therapy, Mayer (1935) appraised the present status of light treatment about as follows: (*a*) Exposure of the entire body to carefully graded doses of sunlight, or proper artificial sources of such light, so that the visible ultraviolet and infra-red rays are all utilized, is undoubtedly beneficial in tuberculosis of the bones and joints, peritoneum, intestines, lymph nodes and larynx. (*b*) Of the several forms of skin tuberculosis only lupus vulgaris responds specifically, scrofuloderma and erythema induratum favorably at times. (*c*) Postoperative sinuses are very responsive, fistulas often resistant. (*d*) Pulmonary tuberculosis *per se* is not an indication for light therapy (Coulter and Carter, 1935, agreed on the basis of their findings, and Mayer reiterated his statement in 1942); stationary pleural tuberculosis is often helped by it. (*e*) The treatment deserves a trial in genito-urinary tuberculosis. (Miller and Lustok, 1939, reported encouraging results from the use of ultraviolet ray therapy in genital tuberculosis in the male.) (*f*) Ocular and aural tuberculosis respond infrequently; oral tuberculosis is most resistant.

Colonel Cooper (1938), summarizing the experience of the Army at its clinic for heliotherapy in Denver, was substantially in agreement with the

above. At this clinic, where treatment was apparently modeled on that of the famous Rollier clinic in Switzerland, the body was divided into the following six zones: ankles, knees, crotch, navel, nipple, chin—exposure being directed to these zones, front and back, in increasing numbers until at the fourteenth day the entire body, front and back, is exposed for the first time. But the exposures have progressed so gradually that this first exposure of the entire body is only for five minutes, front and back; not until the thirtieth day does complete exposure of front and back last a full hour.

Heliotherapy should be applied only under expert guidance, for an overexposure of a tuberculous patient to the sun's rays may be highly toxic and actually induce hemorrhage as the result of a nonspecific perifocal reaction.

Roentgen Therapy.—Light therapy has almost completely superseded roentgen therapy nowadays, but, according to Mayer (see above), the latter may still be the treatment of choice in the infiltrative stage of lymph-node tuberculosis. If employed together with heliotherapy, earlier results are often obtained in tuberculosis of the small bones, superficial joints and skin; Hayes (1941), of the University of Minnesota Hospitals, said that it is the treatment of choice in pelvic tuberculosis of the female. But roentgen therapy should not be employed in any of these instances if there is also present an active pulmonary tuberculosis.

Tuberculin.—The bright hopes which followed Koch's announcement of this substance as a specific remedy in 1890 were soon followed by disappointments so deep that many men today regard any and all types of tuberculin as absolutely worthless, a position which cannot be completely defended because a few *careful* users of the remedy have shown that it has a limited place in therapy. It is certainly in no sense a specific remedy and the number of cases in which it is indicated is very small. The study of Willis (1940) confirmed the opinion that physicians who are not able or willing to make a special study of the treatment should never use tuberculin; the requisite guided experience cannot be gained from the pages of a textbook.

Specific Chemotherapeutic Agents.—The results obtained with chemotherapeutic agents in experimental animals in recent years led to the hope that we would soon have a specific agent for the treatment of the disease in the human. Promin, diasone and promizole have been the most promising agents in animals and a study of these drugs is progressing in the human, but at the present writing the work can only be looked upon as still entirely experimental and not ready for employment by the practitioner.

Diet in General.—The opinion of Banyai, expressed in 1934, was then and is now still corroborated by the experience of all specialists in tuberculosis: (*a*) the ordinary balanced house diet is adequate for the great majority of patients with pulmonary tuberculosis and, other things being equal, will restore the weight to normal; (*b*) increase in weight in those below par should be accomplished primarily by proper attention to the disease itself; (*c*) the use of strange, supplementary, concentrated foods to which the patient is not accustomed is not indicated; (*d*) overfeeding is both unnecessary and unreasonable and may be harmful in that extra weight taxes the pulmonary function; (*e*) milk may upset the digestive system and should not be forced as an accessory food; when included in the diet it is best taken in small sips after meals; (*f*) there is no proof that unusual quantities of eggs are helpful.

Special Dietary Factors.—*Cod Liver Oil.*—This agent has been used in the treatment of tuberculosis for more than a century but the only evidence of its

value is of the nature of clinical impression rather than of proof. It seems to me a significant fact that use of the oil has been abandoned in most sanatoriums, but I shall continue to describe the method of its employment here because some men still feel that it has undoubted value. Cod liver oil, then, is best given two hours after a meal in a daily dose of 1 to 3 ounces (30–90 cc.). Many individuals who are unable to take the distasteful substance in the beginning may be trained up to it by starting with very small doses. If both the oil and the spoon in which it is taken are kept on ice the odor is much lessened. It is said that the eating of a banana immediately after swallowing the oil is most effective in overcoming the objectionable taste and odor and in preventing loss by vomiting. The U.S.P. emulsion, and the emulsions with malt and egg of the N.F., are potent and satisfactorily flavored; the N.F. emulsion with hypophosphites is an unnecessary preparation. The following prescription is a satisfactory working model for the writing of an emulsion, the rules being that there shall be at least one-fourth as much acacia as oil to be emulsified and that the flavoring syrup shall not exceed 10 per cent of the total.

℞	Cod liver oil	℥iv	120.0
	Acacia	℥j	30.0
	Syrup of thyme	ʒvj	24.0
	Water to make	℥viij	240.0
	Label: One or more teaspoonfuls as directed.		

Simple syrup might be substituted for syrup of thyme and flavoring accomplished by addition of 0.4 per cent (of the whole) of the oil of peppermint, spearmint, lemon, orange, or almond. The following formula for an aromatic oil is contained in the Pharmaceutical Recipe Book:

Gluside (saccharin)	0.5
Compound spirit of orange	20.0
Cod liver oil to make	1000.00

Vitamins.—A number of independent observations in recent years have indicated that "exhaustion" of vitamin C occurs in tuberculosis and that the therapeutic use of the vitamin might be worthwhile. Sweany *et al.* (1941), of the Chicago Municipal Tuberculosis Sanatorium, reported an extensive study of the matter, 79 patients being studied for vitamin saturation and 282 in treatment. They found that exhaustion of this vitamin does occur and appears to be proportional to the severity of the disease. Special diets high in vitamin C will prevent or relieve this unsaturation but in rare instances they found it necessary to administer a salt of ascorbic acid intravenously. Their tentative conclusion was that no patient should have less than the standard optimum dosage of 50 to 60 mg. daily and that this quantity should be increased to as much as 200 mg. daily in relationship to the severity, activity and duration of the disease. "Frequently, when the disease is far advanced, patients deficient in vitamin C are benefited by being kept saturated with the vitamin, as shown by a prolongation of life of the treated patients over the controls, as well as slightly more favorable clinical and laboratory observations. Adequate vitamin C is therefore just one of the many factors necessary for a proper treatment of tuberculosis. No benefit was noted in an excess beyond saturation."

Farber and Miller (1943) concluded from their study of 400 patients that 25 per cent of them had deficiencies in nicotinic acid (niacin) and riboflavin. Getz and Koerner (1943) found the level of vitamin A in the plasma of re-

cently diagnosed tuberculous patients lowered in proportion to the extent of the tuberculous involvement, and Banyai and Cadden (1944) felt that there were theoretical reasons for massive vitamin A administration as adjunctive therapy in pulmonary cases, particularly in the presence of diabetes mellitus. It seems to me that someone should attempt to pull together this whole subject of the relationship of the vitamins to tuberculosis and undertake a definitive study of it.

Insulin.—A few years ago a wave of enthusiasm spread over certain circles in the profession for the use of insulin to promote hyperalimentation and weight gain in tuberculosis, but the review of Allen (1936) showed that the many recorded disappointments and mishaps were sufficient to dampen quickly the ardor of most practitioners. This was only to be expected since insulin is a powerful agent and certainly not to be haphazardly used even in healthy individuals, to say nothing of the tuberculous. However, that there is a class of patients in which its careful employment may be of some value has become evident, since it will improve appetite and induce gain in weight in probably the majority of patients not extremely ill or moribund. Dosage with most observers has been between 15 and 60 units distributed throughout the day; the same precautions with regard to shock are of course to be observed here as in diabetes. Since the indications for the use of insulin in selected cases of tuberculosis are anorexia and loss of weight along with the frequently accompanying epigastric symptoms, Spellberg and Rosenblum (1936) made the sound point that it is illogical to use the agent in patients who are gaining weight even though they complain of unsatisfactory appetite; but an occasional patient who is losing weight despite good appetite may benefit from insulin. They listed the following definite contraindications: (*a*) laryngeal involvement when swallowing is painful; (*b*) gastro-intestinal tuberculosis with diarrhea, which the increased food ingestion will aggravate; (*c*) extreme emaciation and exhaustion, when the patient needs help in feeding and is prone to develop severe reaction.

Salt-free (Gerson, Sauerbruch-Hermannsdorfer) Diet.—These diets were evolved in an effort to change the nature of the soil in which the tubercle bacillus lives, though they came originally into use following the fortuitous discovery by the principal proponent (Gerson) of improvement in a case of lupus in whom a salt-free diet was being used for another purpose. The good results in many types of tuberculosis reported by Gerson have not been susceptible of duplication by most other observers, but Dr. Gerson was still indefatigably pursuing the subject in Paris before the outbreak of War II. I think it is now universally acknowledged that this type of dieting is often of great cosmetic benefit in lupus vulgaris, and that oftentimes in renal, and sometimes in bone and joint tuberculosis, it is worth the trial. Pulmonary cases, unresponsive to other treatment, may occasionally be benefited. The diets are quite objectionable to the patient and are so complex in their original form that they are at present looked upon as suitable only for use in institutions where there is complete control of patients and expert dietary supervision. However, Banyai (1934) found that the regular house diet can be made to serve the purpose very well through modification as follows: (*a*) add no salt to dishes and omit canned foods of all kinds as well as smoked and spiced meats, sausage and ham, smoked and salted fish; (*b*) season with curtasal, a nonsodium and chlorine bearing salt substitute; (*c*) give 7 drops of viosterol and 15 grains (1 Gm.) of calcium lactate thrice daily.

Cod Liver Oil as Topical Application.—Banyai (1940) made topical application of this oil in 270 cases; in brief summary he found: (*a*) favorable effects in pharyngeal and laryngeal ulcers and in laryngeal infiltrations with vegetative granulation, but not if there is marked laryngeal edema; (*b*) tuberculous empyema in the absence of bronchopleural fistula responded well to aspiration of pus and replacement by the oil; suppurating lymph nodes were similarly treated with satisfaction; (*c*) in the form of eye drops the oil was unsatisfactory in tuberculous keratitis but of use in phlyctenular conjunctivitis and keratoconjunctivitis cases; (*d*) the oil was of some value in cold abscesses secondary to bone tuberculosis, in fistulas originating from tuberculous epididymitis and in ischiorectal fistulas; (*e*) the results were very good in scrofuloderma and in lupus vulgaris. Banyai and Fitzgerald (1943) concluded that cod liver oil is a useful remedy for the treatment of oral tuberculosis.

Miscellaneous Remedies.—The following agents or methods have all been considered at one time or another to exert some more or less "specific" action, but none of them at present seems to merit a place in the discussion of practical phases of therapy in tuberculosis: Dreyer's defatted antigen; gold sodium thiosulfate (sanocrysin); calcium salts, except in the treatment of intestinal tuberculosis (*q.v.*); iodine or the iodides; cadmium sulfide; creosote and guaiacol; sodium morrhuate; Spengler and Spahlinger treatments.

Fever and Night-sweats.—Under the sanatorium regimen which is being presupposed throughout this entire discussion, these two symptoms usually do not persist in aggravated form long enough to warrant a resort to drugs in their correction. However, when the former is felt to be excessively wasting the patient by its daily high rise it is nearly always possible to forestall it by the use of 5 to 10 grains (0.32–0.65 Gm.) of aspirin or phenacetin, 3 grains (0.2 Gm.) of acetanilid, or 5 grains (0.32 Gm.) of amidopyrine (see Agranulocytosis for toxicology of the last drug). Night-sweats are more difficult to treat. They can sometimes be prevented by the use of atropine sulfate in a dose of 1/200 to 1/100 grain (0.00032–0.00065 Gm.) but frequently at the price of an increase in cough and restlessness; also agaricin may be used in ½ grain (0.032 Gm.) doses in pill or capsule, not more than three of which should be given in the twenty-four hours, but this drug is extremely unreliable in its action. Hare wrote enthusiastically of camphoric acid in a dose of 20 to 30 grains (1.3–2 Gm.) an hour or two before the sweat is expected, repeating the medication once in obstinate cases. Some such formula as the following may be employed:

℞	Camphoric acid	ʒiv	15.0
	Compound tincture cardamom to make	℥vj	180.0

Label: Dessertspoonful (8.0 cc.) to a tablespoonful (16.0 cc.) one hour before sweat is expected.

An alcohol rub at bedtime, or a sponge bath with tepid water to which has been added 15 grains (1 Gm.) of alum per ounce, is also sometimes effective in preventing mild sweats.

Cough.—Here again, as in the case of fever and night-sweats, the rest, which is so important a part of the sanatorium regimen, is the most valuable remedy of all. Many patients succeed in training themselves to control this symptom remarkably well, only permitting themselves to indulge in a thorough "cleaning-out" cough in the morning; but when a wracking cough is disturbing the patient's rest both night and day, some attempt must be made to check it. The reader is referred to the discussion of cough in the article on Common

Cold. Banyai and Cadden (1943) found that the following things may often be accomplished by having the patient inhale a mixture of 10 per cent carbon dioxide and 90 per cent oxygen: (*a*) spells of strenuous exhausting coughing are prevented and thereby rest is secured for the patient and particularly for the lungs; (*b*) an unproductive cough is transformed into a useful one; (*c*) directly after inhalation the amount of expectorated sputum is increased and its character changes from a heavy, thick and tenacious type into a thinner, serous and more watery kind; (*d*) the use of expectorant drugs and narcotics can be reduced.

Hemorrhage.—Keep the patient as quiet as possible with the head propped in such a way that blood will easily flow out of the mouth. Mayer (1942) advised against the use of morphine as it favors spread of the disease through retention of infectious clots. Ice-bags on the chest over the suspected site of the hemorrhage are reassuring; small bits of ice are usually given to be swallowed. Sand-bags on the chest and against the side help to accomplish partial immobilization. Mayer (1942) said that if one can localize the site of the bleeding and has knowledge of the extent of the preceding disease, pneumothorax may be occasionally resorted to in otherwise uncontrollable hemoptyses. However, he felt that the danger of producing atelectasis during active bleeding must be recognized and that collapse of a lung drowned in blood is a questionable procedure at best. He said that occasionally one must resort to phrenic nerve crushing or rarely phrenicectomy when all other measures have failed. Amyl nitrite or nitroglycerin is sometimes used to lower blood pressure, but I think this type of therapy illogical in a patient threatened with shock. Several men have reported the successful use of Congo red. Hemostatics of the usual tissue extract or serum types are of no value. Berghausen (1937) reported 2 cases in which intravenous injection of 30 Gm. of acacia in 500 cc. of physiologic saline was followed by cessation of the bleeding.

In patients who have a long period of blood spitting after the acute hemorrhage, parathyroid extract and hydrastinine hydrochloride have been recommended, but I doubt the rationale of both these measures. Following cessation of the bleeding, diet is restricted to cold dishes and drinks for a while. The use of cathartics or enemas to prevent straining at stool is advisable in some instances.

Care of Digestion.—This is extremely important, for the majority of sufferers from pulmonary tuberculosis have some form of indigestion; it is best accomplished by enjoining slow and thorough mastication and complete rest both before and after meals. Sodium bicarbonate in a dose of 15 grains (1 Gm.), or ½ drachm (2 cc.) of the aromatic spirits of ammonia, the former dissolved in warm but not hot water and the latter to be well diluted before taking, will usually dispose of postprandial distress; or, if these fail, the opposite treatment with dilute hydrochloric acid in a dose of 15 minims (1 cc.) may be indicated. It is extremely doubtful whether pepsin or pancreatin is of any value here. Such simple remedies as the drinking of a little hot water before meals or placing an ice-bag on the abdomen will often relieve nausea. If there is vomiting and much distress during the day an evening lavage of the stomach, using preferably the duodenal tube, may give relief for the night. To stimulate a lagging appetite any one of the following excellent U.S.P. stomachic mixtures, with a dose of 1 teaspoonful before meals, is of value: compound tincture of cardamom, compound tincture of gentian, compound tincture of cinchona, or the tincture of nux vomica in a dose of 15 minims (1 cc.). Also "tonic" mixtures

should not be overlooked; some such capsule as the following may be used for a short time:

℞	Arsenic trioxide	gr. ss	0.03
	Extract of nux vomica	gr. v	0.32
	Quinine sulfate	ʒss	2.00

Make 40 capsules.
Label: One, later two, capsules three times daily after meals.

The full tonic dose is contained in 2 capsules, but the precaution of giving only one the first day will make possible early detection of quinine idiosyncrasy.

Pleuritic Pain.—The pain accompanying pleuritic inflammation is oftentimes very severe and greatly retards the patient's progress. A few cases will respond favorably to counterirritants: two of the small mustard plasters obtainable at drug stores should be used end to end under the arm, so that one extends toward the nipple region in front and the other over the lower part of the scapula behind. Adhesive-plaster strapping is more often effective, applying the straps to the side with the patient in the sitting position and holding the breath after a forced expiration. In an unfortunately large number of cases, however, it is necessary to resort to opiates. Farber (1943) found the injection of procaine a valuable measure; the technic consisted in preliminary barbiturate sedation followed by the injection of approximately 10 cc. of a solution of 1 per cent procaine with 1:25,000 epinephrine hydrochloride into the skin, chest wall and parietal pleura. The relief of pain by the injection of 80 per cent alcohol into the intercostal nerves close to their emergence was also reported a number of years ago.

Laryngeal Pain.—Vocal rest is sheet-anchor therapy, collapse treatment valuable as both preventive and curative agent in laryngeal tuberculosis. For the relief of the excruciating pain which often accompanies deglutition cocaine is used in a spray of 1 to 4 per cent; this is always to be considered dangerous, however. Orthoform, which is an insoluble anesthetic, may be blown into the larynx, but Lockard prefers to use it in the form of an emulsion; he employed the following formula:

Orthoform	12 parts
Menthol	1 part
Almond oil	30 parts
Yolk of egg	25 parts
Water to make	100 parts

This emulsion is too heavy for use in an atomizer, but it can be self-administered through the use of a Yankauer laryngeal medicator. Iodoform is also frequently used by insufflation, but a small amount of talcum must be added to give weight to the otherwise too light powder; it is wise to precede the insufflation with a spray of cocaine to prevent coughing. A number of writers advise the addition of morphine to the powder mixture; Hare used 1/16 grain (0.004 Gm.) to each drachm of iodoform. Another mixture sometimes successfully employed is known as Lake's pigment, the formula of which is:

Lactic acid	50.0
Solution of formaldehyde	7.0
Phenol	10.0
Water to make	100.0

The phenol in this preparation acts as an anodyne but it is usually necessary to precede the first few applications with cocaine. Ulcers and granulations may

also be touched with 5 to 10 per cent formalin in glycerin, preceded by a cocaine spray. Lukens stated that the local application of chaulmoogra oil, without preliminary cocainization, exerts an analgesic action on the larynx which becomes more complete after repeated treatments. Alloway and Lebensohn and Van Poole in some measure confirmed Lukens, but Peers and Shipman warned that the general condition of a febrile patient may possibly be made worse by these treatments; Wilkinson (1932), and Stevenson (1933), did not obtain the satisfactory results they had hoped for, but the latter, reporting again in 1937, found the treatment beneficial in a large proportion of patients when he changed from Indian to Burmese oil, as recommended by Lukens.

Banyai (1938) introduced the method of spraying the larynx three times daily with cod liver oil from an ordinary atomizer; the oil must be warmed before use and the treatment is best given after meals. Banyai's results were good and so too were those of Fox and Wigglesworth (1939). I know other men who have been using this measure with satisfaction.

Galvanocautery, alcohol injection of the superior laryngeal nerve, actual section of the nerve, ionization and tracheotomy are all employed successfully at times by qualified experts.

A number of years ago Dundas-Grant called attention to the following practical point: "I wish, however, to indicate a cause of what patients call 'pain,' the relief from which is anxiously desired. In reality it is a painful 'burning' stiffness of the pharynx caused by the drying and inspissation of mucus on the back wall, and is experienced chiefly on waking. Patients have frequently described the discomfort as severe pain and have been delighted to have it removed by gargling with a little bicarbonate of soda in water, warm if possible, otherwise cold. Such a solution can be put into a thermos flask at night so as to be ready for use when the patient wakes up. I am sure that this condition is overlooked while deeper-lying sources of pain are being sought for. It seems a trifling method of treatment, but it gives great relief and is, of course, available to any practitioner if he only keeps the condition in mind and looks for it."

Intestinal Symptoms.—Until the appearance of Saxtorph's report, in 1918, on the use of calcium chloride as a palliative agent in the treatment of intestinal tuberculosis, we were practically helpless in the presence of the severe abdominal pain, exhausting diarrhea and tenesmus suffered by patients who are the victims of this type of the disease, though it has long been recognized that in some cases surgical procedures are indicated. The value of heliotherapy, more recently recognized, has already been pointed out. Pneumoperitoneum is also sometimes of value in selected cases. The various astringents are practically valueless, and dietetic treatment, even when faithfully persisted in, succeeds only exceptionally. The excellent results reported by McConkey (1930), who administers ½ ounce (15 cc.) of cod liver oil floated on 3 ounces (90 cc.) tomato juice in a small glass, the dose being taken ice cold immediately after each of the regular full hospital meals, have not been confirmed under satisfactory control conditions (Steinbach and Rosenblatt, 1935); nevertheless Banyai (1940) said he frequently obtains good results with this treatment. The opiates are, of course, somewhat effective, but they must be used in very large doses and when they are intermitted the symptoms are oftentimes much aggravated. In calcium chloride, however, we have a really valuable addition to our armamentarium. It is usually given intravenously in a dose of 5 to 10 cc. of a 5 to 10 per cent solution (sterilized in the autoclave) at intervals of three to seven

days; this dose may be repeated as long as necessary, it would seem. Fishberg particularized as follows:

"When the diarrhea in a tuberculous patient is due to dietetic indiscretions, to the catarrhal condition of the intestinal mucous membrane, or to slight intestinal ulceration, an intravenous injection of 5 cc. of a 5 per cent solution of calcium chloride will give prompt relief. When, however, the intestinal symptoms are due to extensive ulcerations—especially to amyloid infiltration of the intestine—the chances of attaining relief of the pain and annoying diarrhea are remote. Similarly, when the abdominal pains are due to irritation of the intestinal mucous membrane by the contents of the intestine, relief may be attained by intravenous injection of calcium chloride. When, however, the pains are due to localized peritonitis over deep intestinal ulcers, or to peritoneal adhesions, which are not uncommon in tuberculous subjects, calcium chloride is impotent to give relief."

It seems that in some instances good results can be obtained by the intramuscular injection of calcium gluconate or in less urgent cases even by the giving of calcium salts by mouth. Hardt *et al.* (1939) found no advantage of one method over the other but felt that ultraviolet irradiation seemed to increase slightly the beneficial effects obtained from the use of calcium.

Crimm *et al.* (1943) reported good results from the use of pectin agar, being led to employ it as a result of the success sometimes following its use in the treatment of diarrhea in children.

Terminal Opiates.—In the terminal stages of many cases the suffering is very severe. Here the opiates in full doses are oftentimes truly a godsend for they enable us to make the last days of these poor unfortunates much less terrible than they would otherwise be. However, the question of expediency often arises, for opium many times prolongs life in such patients, and a truly immense quantity of the costly drug may be required before the awful end is reached.

Psychotherapy.—There is so much talk nowadays of the great value of this method—as though it were *new*, indeed!—that I fear some of us are beginning to believe all of it. Certainly we accomplish very little when our aim is only to gloss over a real psychological conflict with a mere grin. I know not a few persons who revolt temperamentally against the sort of planned cheerfulness that is current. Perhaps the reader may feel that they are then almost certain to die if they come down with tuberculosis—and it may be that they are!

PROPHYLAXIS

From 1922 until it was disturbed by the outbreak of War II, large scale vaccination of infants against tuberculosis was going on in France and in portions of some of the other Continental countries, the aim of this prophylactic attack being not to produce permanent immunity but only to support the child's reactions during the period when natural immunization is taking place. The vaccine used is made from cultures of living bovine bacilli that have been attenuated by growing them for years on bile potato media (Bacillus Calmette-Guérin, or BCG), it being claimed that these organisms are still capable of stimulating antibody production though they have lost their power to produce tuberculosis either in a general or local form. An enormous literature has accumulated upon the subject, which remains highly controversial; the especially interested reader will find the following to be recent significant publications: Guérin (1935), France; Kayne (1936), England; Goodwin (1936), Levine

et al. (1938), United States; Hopkins (1941), Canada; Wallgren (1943), Sweden. Upon the whole, here in America—and I believe I may say as much of England also—the attitude is still one of very cautious skepticism. I shall attempt to expose the chief roots of our conservatism in the following paragraphs.

(*a*) Careful and competent statistical analysis of the French data has failed to convince us that human tuberculosis is effectively prevented by this method.

(*b*) The organism is admittedly capable of producing lesions in the animal body, from which it can be recovered, but it is denied that it can establish active centers of tuberculosis or is able to set up progressive tuberculosis on reinoculation into fresh animals. We do not consider this point of avirulence proved.

(*c*) In Lübeck, during three months in 1930–1931, there were 68 fatalities in infants which were directly traceable to the vaccine. It seems now to be established definitely that the culture sent from Paris to Lübeck was not virulent; but something happened to the culture in Lübeck, though it was never possible to determine what that something was. It is difficult to forget Lübeck, and we want assurances that under proper safeguards (which no one can as yet define) the thing will not occur again.

(*d*) In France there is increasing recognition of the fact that the vaccinated need just as much protection against contamination from openly tuberculous individuals as the nonvaccinated. Wherein, then, lies the advantage of vaccination?

(*e*) A positive tuberculin reaction is admittedly the only evidence that vaccination has been successfully accomplished. But to us the positive tuberculin reaction indicates a state of allergy and connotes, other things being equal, development of the reinfection type of tuberculosis when the individual is subsequently assailed by the bacillus of tuberculosis in adequate numbers. It would seem that the advocates of BCG vaccination rush in to induce in early infancy the same state of allergy which it is the object of our utmost endeavor in this country to prevent.

(*f*) At the beginning of this present article on tuberculosis, I have offered a brief resume of the prophylaxis of the disease as practiced in America: application of the fine-tooth-comb method of finding infectious cases in order that, through their isolation, infants and children may be protected from acquiring first-infection tuberculosis as long as possible. The method is apparently efficacious though costly and not giving any very bright promise of ever eliminating the disease entirely. But hasty adoption of BCG vaccination in the present state of knowledge regarding the true value of this "preventive" measure might really be comparable to swapping horses while crossing a stream.

The studies of Wells and his associates (1944), in Jamaica, suggested that there might be a practical place for a heat-killed vaccine of the sort they employed in certain groups of individuals subjected to unusual risk of tuberculosis infection.

The outbreak of War II terminated for the time being some experimental studies with a vole vaccine in England which were reported to be yielding more promising results than with any methods tried up to this time.

TULAREMIA

(*Rabbit Fever*)

Tularemia is an infectious disease in practically all wild rodents through the whole range in size from mice to raccoons, of deer, coyotes, game birds and indeed even snakes; in fact of all the familiar animals of the United States, whether wild or domesticated, it seems that only the horse, cow, pigeon, chicken and turkey have not as yet been convicted with certainty. Originally considered to be confined to the United States, where it was first described, it is now recognized that the disease is probably world-wide in its distribution. Human beings contract tularemia while dressing the carcasses of infected animals, or through the bite of one of the several flies and ticks which act as vectors, through ingestion of the insufficiently cooked flesh of infected animals, and also probably through the inhalation of the causative organism or its passage into the respiratory tract through implantation in the conjunctival tract. The causative organism, *Pasteurella tularensis*, has been shown to be maintained in standing ponds and disseminated in flowing streams and it is therefore felt that water-borne infection is possible in both man and animal. Infection from handling cured pelts and man-to-man transmission are both exceedingly rare. *P. tularensis* was discovered by McCoy and Chapin in 1912 but the disease in man has been definitely known to be caused by the same organism only since the work of Francis in 1919.

The onset is sudden, with chills and fever, pains all over the body, vomiting, sometimes diarrhea and often cough, and prostration. Pulmonary findings are early manifestations in many cases; Foshay's (1940) collective data showed that pulmonary consolidation had appeared in 107 of 600 cases, pleurisy in 56 and pleural effusions in 18. Usually after the first few days of fever there is a remission of a few days and then another rise which persists, with marked daily remissions of the septic type, until it gradually declines in two to four weeks. In addition to the systemic symptoms, there is usually pustulation and finally ulceration at the site of infection, and the glands draining the area become swollen and painful. In more than half of the cases they too break down but sometimes only during a recurrent adenopathy several months or years after apparent complete recovery. Foshay (1940) said that in about 8 per cent of instances bubo formation does not occur and that in these instances there is also very seldom any discoverable primary lesion. During the second week (occasionally not until the third or fourth week) the serum agglutinates *P. tularensis;* the intradermal test may be positive a week earlier. In laboratory-contracted cases the local and glandular symptoms are absent, probably because the organism is ingested or inhaled in these instances. Convalescence is usually very protracted. Relapses sometimes occur several months to years after apparent recovery, but no true second infection has yet been recorded. Mortality is considered to be about 6 per cent, most deaths occurring at the beginning of the third week in cases which have become of a typhoidal type and in which pneumonic manifestations have been prominent.

THERAPY

In April, 1940, the United States Public Health Service stated that there is no specific treatment for tularemia, a statement which was doubtless carefully considered before it was made. However, Foshay continues to make out a case for the ability of his antiserum—now available from both horses and goats—

to modify the course of the disease. His most recent (1940) report was in the form of a compilation of results obtained by many widely scattered physicians, using the serum in 600 cases with 518 untreated controls. I am obliged to confess that his handling of the data is completely confusing to me, so I can only repeat his statement that his statistical studies confirm the clinical opinion that serum therapy effected significant changes in the course of the disease and in the mortality rate, the most favorable modifications being observed in patients who were treated before the thirteenth day. As was to be expected, serum sickness occurred in slightly over half the cases. Foshay does not advise use of the serum as a routine measure; his indications are the presence of tularemic pneumonia, the typhoidal state, if confusion and delirium supervene and if there is coexisting heart disease. Dosage for adults is 30 cc. intravenously, repeating in eight to twenty-four hours as indicated; in fulminating cases 60 to 90 cc. should be used for the first dose. Reports of the use of quinine, the dyes (Lovia, 1941, gave acriflavine intravenously in dosage of 100 mg. in 250 cc. saline; Byfield *et al.* [1945] gave 10 cc. of a 1:1000 aqueous solution of metaphen intravenously to 1 patient on three consecutive days with results that were inconclusive), iodides, neoarsphenamine, etc., are still very scattered. All of the sulfonamides have been tried of course but it is not apparent that they have been of any value. Winter *et al.* (1937) thought that the twice daily intravenous administration of 20 grains (1.2 Gm.) of sodium salicylate in 1 ounce (30 cc.) of distilled water made their 4 patients with pulmonary involvement less "toxic"; all the patients recovered—in one of these cases, in which there were meningeal symptoms, they felt that daily spinal drainage was definitely beneficial. Convalescent serum has not been considered to be of value up to the present time. Moore *et al.* (1944) reported a case in which there seemed to be striking results from excision of the primary ulcer. Most men experienced in this disease feel that broken down lymph nodes should be undisturbed beyond the use of hot wet dressings, that abscessed nodes should not be incised until they are about to break through the skin, and that excision of such nodes is absolutely contraindicated.

TYPHOID AND PARATYPHOID FEVERS

(*Enteric Fever*)

Typhoid and paratyphoid fevers are acute infectious diseases caused by *Eberthella typhi* and *Salmonella paratyphi-A* and *S. schottmülleri-B*. They are unquestionably separate diseases since an attack of any one of the three does not confer immunity against the other two, a fact which is also true in regard to artificial immunization; nevertheless, they will not be considered as separate clinical entities in this book for the reason that in their symptomatology (save for the relative mildness of the paratyphoids) and their therapeutics they are one and the same. Serologically and bacteriologically they can be distinguished one from the other; at the bedside this differentiation can never be made with certainty. I shall discuss the three under the single designation "typhoid fever."

In typhoid fever the attack is essentially upon the lymphoid tissues of the body, being especially marked by enlargement of the spleen and hyperplasia

and ulceration of the Peyer's patches in the intestine. The majority of those who fall ill of this disease are between the ages of fifteen and thirty. There is usually a prodromal period of about a week, during which there is malaise, headache, loss of appetite and pains all over the body; then the patient goes to bed and the attack is looked upon as definitely established. The fever is considered to be typical in that it rises to its peak—which may be as high as 105° or 106° F. (40.5° or 41.0° C.)—by the end of the first week, remains at this level for a variable period but usually one to two weeks, and then falls gradually during a length of time which is usually twice that required for it to rise; throughout the entire course of the fever there are daily morning remissions of one or more degrees. It should be remarked that there are many variations from this typical fever picture. The pulse, too, is characteristic in that it is much slower than one would be led to expect by the height of the fever and nearly always contains at some time a dicrotic wave. At about the end of the first week the so-called "rose spots" appear, usually only on the abdomen, in crops of 10 or 12. Though present at some time during the course of perhaps 95 per cent of cases it is nevertheless certain that true typhoid does occur without the appearance of these spots; I shall never forget a young practitioner who dramatically renounced a medical career because in one of his early cases a consultant overbore him by diagnosing typhoid fever *without* rose spots. The blood pressure is low throughout the attack. The tongue is clean and red around the border including the tip, and heavily furred in the center. Nosebleed and bronchitis are frequent early symptoms. Distention of the abdomen practically from the beginning was formerly regarded as very characteristic of typhoid, but with the more ample diet now in vogue this symptom is not regularly seen. Constipation is the rule; when diarrhea occurs it is usually of the "pea-soup" variety. Delirium, usually of a canny rather than a violent type, is frequent. Prostration is always great, and in severe cases progresses to the state of stupor known as the "typhoid state," during which the patient lies in a low muttering delirium, eyes open and staring, and hands ceaselessly pulling at the bedclothes. The progressive secondary anemia, formerly so common in typhoid, is not so severe nowadays as it was during the era of starvation treatment. At the height of the disease there often is a leukopenia. The specific agglutination of the organisms by the patient's serum is of diagnostic importance, but the worth of this Widal reaction is considerably lessened by the frequency with which it is negative until as late as the third week and the instances, few to be sure, in which it does not become positive at all. The bacilli are themselves present in the blood during the first week; after that they appear in the stools and often in the urine as well.

The principal complications of typhoid fever are intestinal hemorrhage and perforation, pneumonia and pulmonary abscess, venous thrombosis and ulcerative laryngitis. Relapses, in which all the symptoms reappear after a brief asymptomatic period, are frequent; they are usually less severe and of shorter duration than the initial attack. The mortality from typhoid is now about 10 per cent under the best conditions. Perhaps 50 per cent of the fatalities are due to toxemia, 15 per cent to perforation and subsequent peritonitis, 10 per cent to hemorrhage and 10 per cent to pneumonia; true typhoid meningitis is practically always fatal but this complication is extremely rare.

Case reports of atypical types of typhoid fever have appeared in recent years: typhoid pyelonephritis without symptoms referable to the intestinal tract (Reimann, 1938); uterine bleeding as a prominent symptom (Wofford

et al., 1938, Lantin *et al.*, 1939); cases in which the symptoms of agranulocytosis or of purpura predominated (Lantin *et al.*, 1939); cases with no evidences of intestinal involvement at autopsy (Lantin *et al.*, 1939). Malbin (1940) reported that the vast majority of cases occurring after partial or complete vaccine immunization, seen by him during an outbreak in Spain, showed abbreviated or otherwise atypical courses; this was true also of the seven cases seen by Tullis (1945) in Sicily during War II. Dietrich's (1937) analysis of 60 cases in infants and children revealed a characteristically abrupt onset, the frequent appearance of neurologic symptoms and a shorter course and lower mortality than in adults. Diddle and Stephens (1939) described a case of probable intrauterine typhoid fever in a baby born of a mother convalescent from the disease.

Typhoid fever is undoubtedly a very old disease, but it was long confused with typhus. The belief was formerly held that certain parts of the tropical portions of the globe were free from the disease, but more careful studies of the fevers prevailing in these regions have shown them to be the same typhoid which ravages the rest of the world. The human body is the only natural habitat of the causative organisms and all cases are caused by contact with the feces or urine of an infected individual, whether he be actively infected or a "carrier." This contact may be direct or indirect: through a contaminated water or milk or ice cream supply, by the ingestion of food over which flies have dragged their infected filth, or the eating of oysters which have been infected in their feeding or fattening beds, or even through the medium of ingested dust—this latter method of infection was held responsible for many of the cases in the British Army during the Boer War. Being a filth-borne disease it is to be expected that modern sanitation would have greatly lessened its incidence, and so it has; indeed, the decrease in typhoid in this present century is one of the things of which medical sanitary science has most reason to be proud. For nearly a decade now, the death rate per hundred thousand in representative large cities in the United States has been below 1.0, whereas in 1910 the rate was slightly above 20.0; in a few cities in the South, however, in which the former rate was as high as 35.0 to 50.0, it is still between 3.0 and 4.0.

Typhoid fever, which increases in incidence after June to a peak in late fall and early winter, is by no means the "thing of the past" that it is unfortunately represented to be in some quarters. How this pestilence is lurking about all great cities, ready to swoop down upon the inhabitants when the guard is the least bit relaxed, was amply shown in the Montreal epidemic of the spring and summer of 1927. In a certain portion of that city of approximately a million inhabitants, during a considerable period of time the raw milk from a district outside the city in which sanitary conditions were unsatisfactory was allowed to be distributed without being adequately pasteurized. The result was that there developed in the city, between the approximate dates of March 1 and September 1, a total of 5014 cases of typhoid, 500 of which terminated in death. More recent epidemics have been those at Bournemouth (1936) and Croydon (1937), in England, a severe one in a state hospital for the insane in Illinois (1939) and the one in Melbourne (1943). Trailer camps and eating places along much travelled highways have also scattered cases widely throughout our country in a few instances in recent years. Harvey (1937) felt that perhaps some cases of infection with *Salmonella suipestifer* are mistakenly diagnosed paratyphoid fever because of the frequency with which cross agglutination in test serums may occur.

THERAPY

Dietetics.—Typhoid fever has greatly changed in my time—which is an astonishing thing since no specific remedy has been added to the armamentarium. But changed it has, for I well remember that during my childhood, which was spent in a large city in Kentucky, it was quite as usual for a number of relatives and acquaintances to be hovering about the edge of one's consciousness as gaunt and tottering specters who were "recovering" from typhoid, as it was for all of us to be dosed with quinine during a part of each year. I was twice attacked by the disease (typhoid or paratyphoid? Widals were only beginning to be done then) in my youth, and twice, though neither attack

TABLE 9.—TYPHOID DIET WHICH WILL FURNISH 3000 CALORIES

Breakfast.	Calories.
Farina (4 tablespoonfuls, cooked)	100
Toast (1 slice, 30 Gm. before toasting)	80
Cream, 100 cc. ($3\frac{1}{2}$ ounces) 20 per cent, which is approximately the same as the top 4 inches from a quart bottle of milk that has stood at least six hrs.	200
Butter, 8 Gm.	62
Lactose, 40 Gm. ($1\frac{1}{3}$ ounces). To add lactose to milk, boil 15 Gm. in 30 cc. of water: cool and add to milk	160
Sugar, 20 Gm.	80
Coffee, 1 large cup	00
10 to 10.30 A.M.	
Milk, 200 cc. ($6\frac{2}{3}$ ounces)	140
Cream, 50 cc. ($1\frac{2}{3}$ ounces)	100
Dinner.	
Eggs, 2	150
Potato, 1 medium, about	100
Bread, 1 slice, or roll, 1	80
Butter, 30 Gm. (1 ounce)	234
Apple, 1 medium sized (pared and cored)	234
Sugar, 15 Gm. ($\frac{1}{2}$ ounce)	60
(Potato baked, served with butter. Apple baked with 15 Gm. sugar, and about 8 Gm. butter. Some patients will eat more butter if the unsalted is used.)	
3 to 4 P.M.	Calories.
Tea, 150–200 cc.	00
Lactose, 50 Gm. ($1\frac{2}{3}$ ounces)	200
Sugar, 5 Gm.	20
Cream, 50 cc. ($1\frac{2}{3}$ ounces)	100
Crackers, 3 uneeda or 2 soda, toasted	75
Butter, 8 Gm.	62
Supper.	
Rice, 25 Gm. (1 ounce), boiled	100
Milk, 100 cc. ($3\frac{1}{3}$ ounces)	70
Toast, 30 Gm. (1 slice)	80
Butter, 8 Gm.	62
Sugar, 5 Gm. (for cereal)	20
Cream, 60 cc. (2 ounces)	120
Orange, 1 sliced	100
Sugar, 5 Gm. (with orange)	20
8 to 9 P.M.	
Cocoa, 5 Gm.	25
Sugar, 10 Gm.	40
Milk, 150 cc. (5 ounces)	105
Cream, 30 cc. (1 ounce)	60
Lactose, 25 Gm.	100

was very severe, I had to "learn all over" to walk again. Where are the convalescent ataxics of yesteryear? And why are we so seldom able to show to our students of today the wasted individual with grotesquely protuberant abdomen, exhausting himself in hallucinatory delirium or worse still lying in the low distressing "typhoid state"? Perhaps the organism is becoming less virulent or mass immunity is being built up, but I believe that the true answer lies in the changed attitude toward diet in the treatment of this dread disease. All of which is but a verbose preamble to the following statement: *the introduction of the full diet in the therapeutics of typhoid fever is the greatest contribution of all time toward the therapeutic control of the malady.*

The mind at once leaps to the question, how has it affected mortality? This is of course very difficult to answer statistically, though the studies of Warren Coleman and others seem quite convincing, but it is the almost unanimous clinical impression that full feeding has had much to do with the reduction in the death rate which has occurred in the last few years. Certainly the severity of the symptoms is greatly lessened: extreme tympanites is unusual, and when it occurs can often be overcome by a proper adjustment of the diet; diarrhea often yields in the same way and constipation, on the other hand, is less stubborn because there is actually considerable food residue present to be propelled through the bowel; both delirium and stupor are modified; bed sores are practically a thing of the past; anemia is scarcely ever so profound as on the starvation diet; and what is best of all, the patient leaves the bed very little more wasted than he entered it, thus tremendously reducing the period of convalescence. And if it cannot be proved that the high calorie diet has reduced the incidence of hemorrhage and perforation it certainly cannot be proved that it has increased it either. Relapses seem to be more frequent, however, under the new treatment.

TABLE 10.—TYPHOID DIET WITHOUT MILK

6.30 A.M.	Cup of hot coffee, sugar, 2 drachms (8 Gm.); 2 slices of zwieback or toast, butter.
8.30 A.M.	One portion of oatmeal or Robinson's prepared barley, with 6 buttered crackers, saltines.
10.30 A.M.	6 ounces of soup, various kinds (180 cc.).
12.30 P.M	1 medium baked potato, mashed and prepared with butter and salt; 2 thin slices of buttered toast, hot, and 1 cup of hot weak tea with 2 drachms (8 Gm.) of sugar.
2.30 P.M.	2 teaspoonfuls of pudding, bread or tapioca; 6 saltines.
4.30 P.M.	2 ounces (60 Gm.) of rice, farina or cream of wheat mixed with 1 ounce (30 Gm.) of butter and 4 drachms (16 Gm.) of sugar.
6.30 P.M.	3 slices buttered toast.
8.30 P.M.	6 ounces (180 cc.) of soup.

Proper feeding, then, is the most important element in the treatment of typhoid fever. Indeed, the old difficulty of devising means of reconciling the patient to the exclusive milk diet which was imposed under the old regime has given way to a diametrically opposed problem, namely, that of getting as much food into him as it is now considered desirable for him to take. Four thousand calories per day is perhaps the optimum amount if we are entirely to prevent loss of protein from the tissues, but it is almost impossible for any but convalescent patients to accomplish the daily consumption of this much food; 3000 calories, however, should be possible with skilful nursing. I append one of Coleman's diet lists which will furnish this amount of calories in a day (Table 9).

Of course it is not necessary to determine the quantity of calories accurately; the idea is to get as many into the patient as possible. Simple diarrheas will usually respond to an adjustment of the amount of cream (fat) allowed; sometimes the lactose has also to be reduced. It is well to bear in mind that if a patient has aversion for particular foods when well he will continue to dislike them when ill. Schoffman (1941) thought that the use of large amounts of ripe banana was provocative of good results in a small number of cases in children. Some patients cannot tolerate milk in any form or amount. For such, Garton devised a diet which, according to Wisart *et al.*, is used in the University of Michigan Hospital in the form given in Table 10.

Care of Mouth and Skin.—The tongue and mouth tend to become very foul, and the lips cracked and sore, in typhoid fever. The teeth should be kept well brushed and the mouth washed at sufficient intervals with the N.F. alkaline aromatic solution; it is well to anoint the lips with glycerin and water. A daily cleansing bath with soap and water should be given, to be followed by an alcohol rub; areas especially liable to the development of bed sores should have alcohol applied to them several times daily and be kept well powdered in the interim. These things have a double purpose: first, they make for the greater comfort of the patient and serve the ends of ordinary cleanliness, and second, they serve to keep up the morale of the patient; to this latter end he should be encouraged to participate actively in the daily routine procedures as much as is possible consistently with the avoidance of fatigue.

Control of Temperature.—The new tendency in the therapy of all acute fevers is to look upon the rise in temperature as a physiologic process and to direct no drug treatment toward its reduction, and undoubtedly many lives have been thus saved; but I cannot hold with the extremists who would totally disregard all antipyretic measures. External hydrotherapy seems to me a wholly rational and nondangerous measure; not the Brand bath, nor perhaps even any of its modifications, but tepid sponge baths with water and alcohol, two parts to one, when the temperature reaches 102.5° to 103° F. (39.4° C.), and a carefully applied cold pack (the patient to be placed on two blankets which are doubled lengthwise of the bed under his body, then quickly enveloped to include the arms in a sheet which has been wrung out of cold water, and thoroughly wrapped round with the blankets which are brought up from each side and overlapped) when the temperature becomes excessively high. We were formerly allowed to believe that this shock, with the warm glow which subsequently spreads over the body, acts as a tonic to the circulatory apparatus; now there are those who cavil at this, but for my own part I still believe that these packs are "stimulant."

Fluids, Chlorides and Vitamins.—Since the patient has fever and is losing a considerable amount of water and salt in consequence, fluids should be given liberally and salt added in considerable quantity to the food or given in the form of the commercial tablets. Most patients will take lemon- or orangeade when they rebel at plain water. When the patient's interest cannot be sufficiently aroused to ensure the taking of fluids by mouth, resort should be had to hypodermoclysis or proctoclysis with physiologic saline solution. If an adequate diet is not being taken, of course it will become necessary if this state persists very long to begin administration of vitamins in concentrated form.

Care of the Bowels.—Typhoid fever most certainly cannot be "flushed out of the system," and it would therefore seem, with the ever-present danger of perforation, that we are well advised to leave the peristalsis stimulators out of the picture altogether. On the full diet treatment, a small soapsuds, or better still physiologic saline, enema at a regular time each morning accomplishes the daily evacuation of the rectum, and what more is needed? Many men have relinquished the old favorite, castor oil, but use instead cascara sagrada frequently throughout the course of the disease; however, even this mild emodin cathartic may at times violently stimulate peristalsis. Liquid petrolatum has enjoyed some vogue of late, but I wonder if we will not conclude in time that whatever good may accrue from the employment of this intestinal lubricant is more than counterbalanced by the increased dissemination of the bacilli incident upon the constant leakage of the oil from the rectum.

Diarrhea.—On the full feeding regimen diarrhea is seldom a prominent symptom and when it does occur usually yields to a careful readjustment in the cream and lactose portions of the diet; when it persists, resort is usually had to the tannins or to bismuth. Acetyltannic acid (tannigen) may be given in a dose of 3 to 10 grains (0.2–0.6 Gm.), four times per day, taken dry on the tongue followed by a swallow of water, or mixed with food, avoiding warm or alkaline liquids. Protan is given in 5-grain (0.3 Gm.) tablets, from 2 to 6 of which may be given at intervals of two hours or more. Albumin tannate (albutannin or tannalbin) must be given in doses of 30 grains (2 Gm.) or more, in capsules or as a powder. For the employment of bismuth the following is a satisfactory prescription:

℞	Bismuth subcarbonate	ʒj	30.0
	Glycerin	℥ss	15.0
	Syrup of ginger to make	℥iv	120.0
	Label: 1 teaspoonful every two hours for 10 doses.		

It is well to avoid the use of opiates in typhoid if possible for the reason that meteorism is likely to follow their withdrawal.

Tympanites.—When this symptom does not yield to dietary adjustment it should be treated as described in the discussion of pneumonia, though of course resort must never be had to pituitrin as there mentioned.

Delirium.—Dissuasion is the best sedative in the treatment of typhoid delirium, but it must be painstakingly and tirelessly employed. When resort to drugs becomes necessary, one of the barbiturates may be used (see list under Insomnia). The following is also a useful sedative prescription, which is not to be used carelessly however:

℞	Sodium bromide	ʒvij	28.0
	Chloral hydrate	ʒvij	28.0
	Peppermint water to make	℥iv	120.0
	Label: 1 teaspoonful in water every three or four hours.		

In rare cases nowadays is it necessary to apply a restraining sheet, though its more frequent use in the muttering, restless, but not actively delirious state of severe cases would doubtless save much of the patient's strength.

Circulation.—The serious cardiovascular complications of the old classical form of typhoid fever are no longer seen in these days of adequate feeding. When there is occasional need for a drug, however, metrazol is probably the drug of choice. One should perhaps note, too, that many men still prefer $\frac{1}{2}$ to 1 ounce (15–30 cc.) of whiskey, three or more times daily, for "stimulation" in typhoid fever.

Specific Serum.—As the result of the work of Felix and his associates, a so-called "Vi + O" antityphoid serum has been made available; it is considered that in this serum two antibodies have been effectively combined, the "Vi" element conferring protection by suppressing the multiplication of virulent strains of *E. typhi* and the "O" antibody neutralizing the endotoxin of that organism. Clinical trials of this new antityphoid serum have been reported from Palestine, Ireland, England, South Africa, China, India and Malaya. The most recent report which has come to my attention, that of Hodgson (1944), who used the serum in 25 cases in Liverpool, indicated that the agent is probably effective in reducing the severity of such symptoms as may be due to "toxemia"; but it would certainly be highly desirable to have a large-scale

alternate case study with this serum before forming an opinion with regard to it. The serum, not available as yet in the United States as far as I am aware, is usually given in doses of 33 to 66 cc. intramuscularly on three successive days beginning at the earliest available moment. Serum sickness of course occurs in most of the cases.

Bacteriophage.—Heeren and Di Lorenzo (1943), in the United States, reported that the use of strain specific bacteriophage had shortened the period of clinical illness in their 7 cases, but Napier *et al.* (1943), in India, reported the administration of the agent without any effect whatsoever in 8 cases; this sort of conflicting evidence is quite characteristic of the whole of the literature on bacteriophage, a substance which has been before the profession for a long time and still has a very doubtful value.

Sulfonamides.—All of the drugs of this group have been tried in typhoid fever and there is no evidence that any of them has value.

Tin.—In Palestine, Reitler and Marberg (1943) employed this element in the treatment of 100 selected severe cases of typhoid fever with a control group of 428 cases of all stages of severity; in the tin-treated cases the mortality was 3 per cent and in the controls it was 8.2 per cent. The controls were not a simultaneously observed group but rather a group of patients treated in the hospital during the preceding year, but it was said that there were no differences in the general character of the disease during the two periods and that the various age classes were equally represented in both groups. The agent was given in tablets containing colloidal metallic tin and tin stearate, the number of tablets administered per day varying from 4 to 20 according to the age of the patient. This work is of course still entirely experimental but it seems interesting, especially as the use of the tin was not associated with the occurrence of any toxic reactions.

Hemorrhage.—Keep the patient absolutely quiet by the use of morphine sulfate, $\frac{1}{8}$ to $\frac{1}{4}$ grain (0.008–0.015 Gm.), or dilaudid, 1/32 grain (0.002 Gm.), every three or four hours; this will also splint the bowel. Withhold all food, and nearly all water, until the bleeding has apparently stopped. Apply continuous cold to the abdomen. Hemostatics are of no value.

Perforation.—Surgical intervention as soon as the diagnosis is made—which is easy to write but difficult of accomplishment for the reason that the diagnosis is oftentimes extremely hard to arrive at and very often a surgeon *with the skill here needed* is not at hand.

Tonics.—Iron, arsenic and strychnine are frequently given during convalescence; I wonder how much they are worth? Some such prescription as the following may be used for a short time:

℞	Arsenic trioxide	gr. ss	0.03
	Extract of nux vomica	gr. v	0.32
	Reduced iron	gr. xxx	2.00

Make 20 capsules.
Label: 1 capsule three times daily after meals.

PROPHYLAXIS

The prevention of typhoid fever groups itself into three subdivisions, in addition to those measures in public health sanitation which are so largely responsible for the reduction in the incidence of the disease in recent years: (*a*) the care of the patient, (*b*) treatment of the "carrier" and (*c*) preventive inoculation.

Care of the Patient.—Everything and everybody coming in contact with the typhoid patient should be considered potentially contaminated. Of course subsequent sterilization of all these objects and persons is a practical impossibility, but it may be approximated by maintaining a state of the most absolute cleanliness in the room or ward, by screening out and exterminating flies, by insisting that the attendants frequently change their clothing and wash and disinfect their hands, and by frequently changing the patient's clothing and bed linen. All clothing and bed linen are to be boiled thoroughly after each use. The patient is to have individual dishes, which are to be boiled after each use. It is doubtful to what extent thorough disinfection of the feces and urine is accomplished, but any one of the following substances should be added to, and thoroughly mixed with, the contents of the bed pan and urinal before it is emptied into the toilet or privy: chloride of lime solution ($\frac{1}{2}$ pound to the gallon of water will make a satisfactory solution provided the lime contains enough chlorine to irritate the eyes markedly when brought near the face; otherwise much more must be used); 5 per cent phenol solution; 5 per cent compound cresol solution; 5 per cent solution of sodium hypochlorite (antiformin). The odor and irritating properties of formaldehyde are too great to make its use practicable. When the urinal and bed pan are not in use one of these solutions, or a 1:1000 solution of bichloride of mercury, should be allowed to stand in it; in some hospitals it is possible to sterilize these articles completely with live steam, a thing not possible of course in the home.

Treatment of the "Carrier."—The vast strides taken in recent decades in the prevention of typhoid fever through measures of public health control have again brought the typhoid carrier to the forefront in many regions where contaminated water or milk supplies, or other unsanitary conditions, have practically ceased to exist as channels of dissemination of the disease. Of course the decline in incidence of typhoid has inevitably reduced the number of carriers, and as this declining number of carriers is itself reduced through death from intercurrent disease, the population is tending to sterilize itself by a combination of the several processes. So the carrier problem, though now probably one of greater importance in specific instances than ever before because of the fact that these reservoirs of infection remain the only sources of contamination in many areas, is upon the whole a problem of declining magnitude. The highly interesting studies of Anderson (1936) and his associates of the Massachusetts Department of Health suggested that contrary to previous belief the more recently a carrier has become such the greater menace he is in general; *i.e.*, the carrier of many years' standing has so infected or immunized the immediate environment that new cases will not develop until fresh susceptible material is introduced, or until such a carrier in later life is obliged to go roaming and is placed in dangerous juxtaposition, as through a food-handling position, to a fresh population.

There are many more reports of failures than of successes through the use of any of the sulfonamides. A few years ago the employment of soluble iodophthalein as used intravenously for gallbladder visualization had a very short-lived popularity.

It seems to be currently the opinion that cholecystectomy for the removal of "nests" of bacilli in the gallbladder is of established value, though only a few years ago the measure was looked upon with considerable disfavor. Saphir *et al.* (1942) felt that treatment with soluble iodophthalein should always be given consideration before cholecystectomy is resorted to, and particularly in

bile carriers past fifty and in the presence of a well functioning gallbladder, since in their use of the agent in 65 bile carriers, the bile was sterilized in 32.3 per cent and the stool was freed from typhoid bacilli in 7.6 per cent. Saphir *et al.* gave their patients 60 grains (4 Gm.) of soluble iodophthalein orally in orange juice three times a week until a total of 40 doses had been given, the patients being kept on a low-fat diet to avoid if possible unnecessary contractions of the gallbladder. The dye was given in the early morning as it was felt that in this way the maximum dye concentration in the gallbladder would be reached at night when repose and the absence of food intake would permit gallbladder rest.

Of one fact we have no doubt: the detected carrier must be trained in personal hygiene and prevented from engaging in food-handling occupations—measures which, if they can be enforced, are probably sufficient in themselves to protect the family and community.

Preventive Inoculation.—War I conclusively proved the worth of prophylactic vaccination against typhoid and paratyphoid fevers, and experience in civilian life all over the world (for example, in the C.C.C. camps, as reported by Lull, 1936) since that war, together with that accumulating in War II, has continued to add to the favorable evidence. For a time the monovalent vaccine, *i.e.*, containing killed typhoid organisms but no paratyphoids, was preferred because it was felt that paratyphoid fever incidence was very low and the omission of these organisms markedly decreased the number of systemic reactions to vaccination. However, paratyphoid cases did occur during this period and the swing has now set in back toward the triple vaccine containing the typhoid and the two paratyphoid organisms. It is this triple vaccine which is being used in our Army at present. The studies of various workers with an intracutaneous method of administering ordinary vaccine have shown that the method is still entirely in the experimental stage. Attempts to confer protective passive immunization of a temporary nature by use of the Felix antiserum previously referred to have not made much headway and indeed cannot be expected to have a great deal to offer under ordinary circumstances. For many years the method of immunization by the oral route, as advocated by Besredka, has been on trial in various parts of the world, but in spite of the vast amount of literature which has appeared in support of this method, the medical corps of none of the world's present great armies (so far as I am aware) has been convinced to the point of substituting the oral for the injection method despite the admitted ease of administration and freedom from reactions of the latter. The oral route having had so long a trial and still being without a secure place should afford sufficient evidence to warrant the general practitioner's adhering yet awhile to the injection technic.

The injections are made subcutaneously (*not* intramuscularly) in the deltoid region at intervals of about a week. There is nearly always a local reaction of some severity; if, for any reason, the abdomen has been chosen for the injections, a more painful reaction must be expected even than that which occurs in the arm, and the reaction in the thigh is so severe as practically to contraindicate the use of this site. The general reaction, which follows in six to ten hours after the injection, is characterized by chills and fever, backache, headache, muscular pains, and in some cases nausea and vomiting and even diarrhea. Most individuals experience some degree of this reaction after one or more (usually the middle) injections, but it usually lasts not more than

twenty-four hours and can be minimized by remaining inactive after the injection.

After the fifth month of pregnancy women are usually not vaccinated, nor are menstruating women, nor infants under two years. Lopez-Rizal, Arguelles and Lara, in Manila, showed that nursing infants are immunized by vaccinating the mother. Nephritis, endocarditis and fever from any cause whatsoever are looked upon as contraindications to vaccination. Expert opinion now seems to hold that it is prudent to refrain from vaccination in all cases of active tuberculosis and in all "arrested" cases unless the danger of typhoid itself is very great.

The adult dose is 0.5 cc. for the first injection and 1 cc. for each of the two subsequent injections. I find three "rules" for dosage in children above two years: (*a*) Adjust the dose accordingly as the weight varies from that of the average adult, taken to be 150 pounds. (*b*) One twentieth of adult dose between two and four, and $\frac{1}{4}$ between four and twelve years (British Med. Assoc. Special Committee Report, June 22, 1935). (*c*) Children over eight years, full adult dose; under eight years, $\frac{2}{3}$ adult dose (Sanford, 1936). As a rule children experience no reactions or only mild ones.

Maximum protection is certainly had within two or at most three months but there is apparently some response within a few days, as indicated by study of the agglutinin titer of the serum. From time to time doubt has been expressed of the advisability of vaccinating in the presence of an epidemic because of the alleged "negative phase" resulting from the inoculation, but the only controlled clinical experiment on this point of which I am aware—the study of Ramsey, in 1935—showed that certainly after completion of the three injections, *i.e.*, after two weeks, but doubtfully after only one or two injections, *i.e.*, after only one week, the case incidence was significantly reduced. Schutze's (1939) animal experimentation certainly yielded evidence in support of vaccination during an epidemic. For the allegation that cases developing in spite of vaccination are milder than they would otherwise have been, I know of no real support from controlled observation.

It is not yet definitely known how long immunity lasts after typhoid vaccination. Longfellow and Luippold's (1940) mouse protection tests indicated that revaccination of the human with a single dose of 0.1 cc. of vaccine intracutaneously (relative freedom from reactions), or 0.5 cc. subcutaneously, reliably renews immunity and that such revaccination should preferably take place each year and certainly at not longer than two-year intervals. According to Long (1944), it is the practice in the United States Army to maintain immunity by the subcutaneous administration of 0.5 cc. of the vaccine each year; a similar dose is administered in the event of actual or potential exposure to typhoid or paratyphoid fever.

VINCENT'S ANGINA

(*Fusospirillosis, Trench Mouth*)

This is an acute infectious disease which seems to have been endemic throughout the world for a long time but was not forcibly brought to the attention of more than a few physicians and dentists until it became epidemic

in the armies during War I, since which time it has been recognized with increasing frequency among the civilian populations of all countries. There have been no reports of widespread epidemics during War II. Vincent's angina is primarily an affection of the tonsillar area and pharynx, the floor of the mouth, the gums about the teeth, and more rarely of the tongue, lips and cheeks. The mouth lesions are single or multiple small red areas which become gray sloughing patches and finally ulcerate and are covered with a yellowish-gray pseudomembrane; the latter is easily removed and displays a bleeding surface beneath, but it soon becomes covered over again. The breath has nearly always a fetid odor and the interference with eating may be great due to the pain of chewing and swallowing; there is often an adenitis, but only in exceptional cases are there very marked constitutional symptoms in adults. Note should be taken, however, of Goldman and Kully's (1933) report of 7 fatal cases in the Cincinnati General Hospital from 1929 through the first six months of 1932; in 6 of the cases there was very extensive ulceration which likely offered a portal of entry for other organisms; in the seventh case edema and sepsis played prominent roles. Black (1938) presented the malady in young children as an acute febrile affair with considerable constitutional reaction but a benign and self-limited course.

Pulmonary complications, often confused with pulmonary tuberculosis, are being recognized with increasing frequency; they may take the form of pulmonary gangrene or abscess, ulceration of the bronchi, lobar pneumonia, bronchopneumonia, or empyema; apparently the disease may also appear primarily in the lungs. Infection of mucous membranes other than those of the respiratory passages, and recovery of the organisms from the parenchymatous organs, has been reported numerous times. Both a spirillum and a fusiform bacillus are easily found in stained smears from the lesions. Whether these are pleomorphic forms of a single organism, or whether they are really two distinct organisms living in symbiosis, is still a moot point; indeed the fusiform bacillus at least is more than likely a normal inhabitant of the healthy mouth, and some observers doubt the causative role of either the bacillus or the spirillum in the disease.

In every case of suspected Vincent's angina, blood study should be performed to make sure that the patient is not really suffering from agranulocytosis.

THERAPY

Sulfonamides.—Fellows (1943) obtained good results in 36 cases of Vincent's angina through the oral administration of sulfathiazole together with the topical application of a saturated solution of neoarsphenamine in glycerin. Linton (1943) obtained highly satisfactory results in 4 cases treated with sulfathiazole dissolved on the tongue, and Manson and Craig (1945) obtained excellent results in 48 cases so treated. Manson and Craig had their patients dissolve a $7\frac{1}{2}$ grain (0.5 Gm.) sulfathiazole tablet on the tongue every two hours during the day and two such tablets every four hours at night. In their series the temperature usually returned to normal in twenty-four hours and the symptoms had almost completely disappeared by that time, but in spite of this treatment was continued for a total of seventy-two hours except in very mild cases in which it was terminated at the end of forty-eight hours. In all cases lesions were cleared up in ninety-six hours after beginning treatment.

Penicillin.—Sweeney *et al.* (1945) reported the employment of this agent in

the U. S. Army during War II in 43 patients. Administration was intramuscular in doses of 25,000 units every three hours, the average total dose being 721,000 units. All of the patients were said to have been cured, though the interesting and unexplained phenomenon of a rise in temperature during the time that penicillin was being administered was reported. Schuessler and Fairchild (1945), also in the Army, used penicillin locally. The ulcer areas were dried and drops of concentrated penicillin (100,000 units per cubic centimeter) were applied to them. After two minutes, 6 cc. of a spray containing 300 units of penicillin per cubic centimeter were applied. These treatments were given at four-hour intervals three times during the day, spraying the mouth with water to remove the debris before each treatment. Cure was said to have been effected in all of the 32 patients treated in this way, the average time required being forty-six hours.

Of course if these good results with the sulfonamides, and particularly with penicillin, are confirmed, all the other types of treatment discussed below will become obsolete; in this edition, however, I am still including them.

Hydrogen Peroxide.—Farrell and McNichols (1937), in a review of their 794 cases, stated that hydrogen peroxide is the most important agent in treatment, all other substances being only adjuvant. They used it in all cases, four or more times daily, full strength. Many men agree that the drug is good but do not employ such heroic therapy, preferring to dilute the agent with at least one part of water. Field (1940) diluted with one part of *hot* water but said that care must be taken not to produce chemical burns with this solution.

Zinc Peroxide.—Meleney (1938) and a number of others have preferred this agent, making a paste of the powder for local application and using 1 part drug to 4 parts water for a mouth wash. Many men prefer this agent, making a paste of the powder for local application and using 1 part drug to 4 parts water for a mouth wash. Longhurst (1943) reported an average time to cure of ten days in 53 patients in whom he had used zinc peroxide.

Sodium Perborate.—This agent was extensively employed during War I and later popularized in the United States by Bloodgood at Johns Hopkins Hospital. A thick paste was made with water and smeared over the teeth and the lesions with the fingers. After five minutes the mouth was rinsed out with water. In some instances a dilute solution was used as a gargle. Fantus (1935) offered the following prescription for an aromatic preparation of the perborate:

℞	Gluside (saccharine)	gr. $\frac{1}{6}$	0.01
	Oil of peppermint	♏x	0.60
	Sodium perborate	℥j	30.00
	Label: Teaspoonful or two in tumblerful of warm water as mouth wash or gargle.		

Not many men were able to obtain the results Bloodgood so enthusiastically claimed, but many did see a considerable number of chemical burns with the perborate and it was finally realized also that the substance is very unstable and that lots of it vary greatly in strength. This drug is therefore not nearly so popular now as formerly.

Arsphenamine, Neoarsphenamine, or Mapharsen Locally.—Many men use one of the preceding oxidizing agents as a mouth wash and then after rinsing the mouth dip a moistened cotton applicator into one of the above arsenicals and rub the particles into the lesions, or else they apply the drug in 10 per cent solution in glucose or glycerin. I quote Barker on the method of getting the powder between the teeth:

"The application of arsphenamine in these spaces is accomplished with facility by taking pieces of coarse knitting wool about 2 inches long, moistening them with water, and dipping them in the powdered salvarsan. These bits of yarn are threaded between the teeth and sawed back and forth after the manner of dental floss, and are then allowed to remain in place for from fifteen minutes to half an hour."

The entire treatment, consisting of the cleansing with an oxidizing agent, the washing out of the oxidizing agent, and the rubbing in of the arsenical, should be employed two or three times daily in severe cases. No harm will be done if small amounts of these arsenical preparations are swallowed.

Arsenicals Parenterally.—These drugs are usually given in smaller doses than are employed in the treatment of syphilis. It should be noted that Vincent's angina has been known to appear and become quite severe in persons who were at the time undergoing routine intravenous arsenical treatment for syphilis.

In the pulmonary cases, any of the organic arsenicals are used as in the treatment of syphilis. Excellent results were reported by some of the earlier workers, but Field (1940) seemed to doubt these results and said that he could not confirm them in his own cases, the number of which was not stated.

Bismuth and Antimony.—There are reports of the successful use of both these agents, the former as in syphilis, the latter as in kala-azar or in bilharziasis (see Index for all these diseases).

Bowman's Solution.—This is a mixture of wine of ipecac, ½ ounce (16 cc.), glycerin, 1 drachm (4 cc.), and solution of potassium arsenite to make 1 ounce (32 cc.). In mild cases this preparation seems to effect a cure if a few drops are used on a soft toothbrush with thorough scrubbing several times a day, and in more severe cases it is good adjunct treatment. One has to be a bit careful with it, however, for some of the potassium arsenite solution (Fowler's solution) may be swallowed, or it is conceivable that quite large amounts of it might be absorbed through eroded surfaces.

Miscellaneous Agents for Local Application.—Practically all the antiseptics and disinfectants have at one time or another been advocated for local use in this disease. Those which have had the greatest vogue are tincture of iodine, 5 to 10 per cent chromic acid, 10 per cent silver nitrate, 2 per cent zinc chloride, 1 per cent potassium permanganate, 2 per cent methylene blue, 1 per cent acriflavine (trypaflavine), hexylresorcinol (ST–37) solution, and potassium chlorate in saturated solution. The results obtained with these substances do not warrant special mention here. The careful studies of Reasoner and Gill, as long ago as 1927, showed that solutions of ordinary toilet soaps, as well as pure soaps prepared in the laboratory, have a definite spirocheticidal effect, and that their use in dentifrices assists in keeping the oral cavity free from mouth spirochetes, thereby affording a measure of protection against tissue infection with the Vincent organisms.

Nicotinic Acid.—Because of the presence of large numbers of fusiform bacilli in pellagrous stomatitis, King (1940) administered nicotinic acid with excellent results in 34 cases. He gave from 60 to 250 mg. of the drug daily by mouth. Schwartzman and Grossman (1941) also found this vitamin beneficial.

Ascorbic Acid (Vitamin C).—Because of existing experimental evidence that low ascorbic acid levels might be associated with infections of this type, Field (1940) suggested that in critical situations 2.5 Gm. of this substance be administered intravenously in doses of 0.5 Gm. spread out through twenty.

four to thirty-six hours; large amounts of the vitamin from natural sources such as oranges and lemons should also be given. Kent (1943), writing of the treatment of Vincent's angina in soldiers during War II, said that ascorbic acid in large dosage should constitute a routine part of the treatment; he advised 0.6 Gm. daily for the first week and subsequently 0.3 Gm. daily.

WHOOPING COUGH

(*Pertussis*)

Whooping cough is an acute infectious disease which we now believe is probably caused by *Hemophilus pertussis*. It is highly communicable and is therefore principally seen in very young children; nearly 50 per cent of cases are in infants under two years of age. There is no distinctive gross or microscopic pathology and the disease is therefore looked upon as one which remains local throughout its course. One attack is almost universally considered to confer life-long immunity, most observers looking upon the exceedingly rare second infections as really first infections in individuals who did not truly have whooping cough the "first" time. There are apparently a great many persons who possess a natural immunity to the disease.

There is an incubation period of three to twenty days and then another week or two during which the symptoms are those of coryza and bronchitis with cough. Gradually during the latter part of this period the paroxysmal nature of this cough becomes apparent and clinical diagnosis is then possible. The paroxysmal stage is characterized by a very distinctive group of symptoms. The patient usually clutches at something for support and then begins a series of rapid, short, loud coughs, during which the tongue is protruded from the mouth, the eyes water and become injected, and the face is suffused or deeply cyanotic, and at the end of which there is a deep inspiration through the narrowed glottis, which causes the "whooping" sound (paroxysmal sneezing in rare instances may apparently replace coughing). In most cases there are several such attacks in quick succession, but they cease at once for the time being when a little mass of glairy mucus is brought up. There is often vomiting during the seizure and many times bleeding from the nose and other mucous membranes. The subconjunctival hemorrhages which occur are usually ascribed to the violence of the coughing. Altogether the attacks are a distressing thing to witness as well as to experience. Between paroxysms the patients, if old enough, are sufficiently undisturbed to engage in their customary amount of activity provided the case is of average severity. The "whooping" period usually lasts from three to six weeks but in many cases it is protracted for a much longer period; it subsides finally into a subacute bronchitis which often persists for many months. In the city of Milwaukee during a ten-year period the average whooping cough mortality, as published by Fox and Knott (1944), was 0.25 per cent; but it is noteworthy that among the more critically ill cases admitted to the isolation hospital during that time there was a mortality of 8.6 per cent among 362 patients, 23 of the 31 fatalities being in infants less than one year of age. Bronchopneumonia is the complication that accounts for most of the deaths. Cardiac complications are rare. Nelson's (1939) thorough review indicated that neurological complications occur perhaps more frequently

than has been thought. Meningeal or other hemorrhage due to violent coughing is a rare complication in children but one that is very dire in its results. Lurie and Levy (1942) felt their study of 500 problem children justified the conclusion that whooping cough occurring early in infancy may lead to the development of severe psychopathologic conditions later in life. Of course there is a greater likelihood of hemorrhage in adults, which makes us always apprehensive upon diagnosing whooping cough in one of advanced years. Surprisingly, whooping cough does not seem to be as harmful in active tuberculosis as one would think it should be.

The disease is transmissible throughout the prodromal period and up to and including the first part—but just how much of the first part, is not known—of the whooping period. Many departments of health in the United States require that the child be kept out of school until he no longer whoops, but elsewhere, notably in France and Denmark, he is permitted to return after he has been whooping for four weeks; in England it seems that the period recommended is six weeks. The finding of the organism by the "cough-plate" method is considered a valuable aid in establishing diagnosis before the whoop appears, though Bullowa *et al.* (1944) and Silverthorne *et al.* (1945) concluded that the employment of the nasopharyngeal swab in combination with a cough plate is of distinct advantage. During and after the second week there is nearly always a relative and absolute lymphocytosis. Flosdorf *et al.* (1943) felt that the skin test utilizing purified pertussis agglutinogen as reagent classifies immune and susceptible individuals and is also useful as a means of stimulating immunity following primary vaccination; more work will be required before one can be certain of these things.

Whooping cough was apparently unknown to the ancients nor is it mentioned by physicians of the Middle Ages. De Baillou described the first epidemic in Paris in 1578. By the middle of the eighteenth century it was widespread throughout the civilized world. It reached the Western Hemisphere in 1732, but for some strange reason Australia escaped until 1890. The disease is very mild in the tropics.

THERAPY

There are two measures of paramount importance in the treatment of whooping cough. First, the child should be kept out of doors as much as possible, for in this way far better than any other will the number of paroxysms be reduced. While not denying the influence of fresh air in bringing about this effect, I am inclined to believe that a more important factor is the child's immersion of himself in enjoyable play. Who has not seen a little tot trudging a weary circuit of the park hand in hand with a bored nurse, who had to assist him through a cough and vomit at short intervals, while a group of nearby children, kept out of school by the same disease, were merrily romping past some of their attacks? Confinement within doors, or attachment to the apron strings without doors, is an irksome thing to the normal robust child; irksomeness makes for irritability, and irritability undoubtedly increases the number of paroxysms in whooping cough. Of course we cannot put very young or very puny children out of doors, so for them the best we can do is to provide adequate ventilation of the house and change them about from room to room for diversion.

The second matter of great importance is the feeding of the patient, for the frequent vomiting in severe cases often brings about a state of malnutrition

almost before we realize it. To treat of this phase of the subject adequately would carry me into the field of infant feeding where I certainly am not qualified to go, nor would such an excursion be fairly within the scope of this book. Suffice it to say, therefore, that a radical reduction in the amount of fluids, and the replacing of the regular feeding periods by a number of small feedings at short intervals between the paroxysms, is usually provocative of good results in children of all ages.

Of drugs and biologicals I must necessarily have much to say because the subject cannot be summarily dismissed, but I would wish to preface what follows with a tripart statement: (1) There is as yet in whooping cough no remedial agent that even approaches specific value. (2) Other things being equal, turning the child free out of doors in mild cases, and carefully nursing him, *i.e.*, providing comfort and nutrition and diversion and sharply watching for complications and emergencies in severe cases, are the simple mandates in the handling of the disease. (3) The fewer drugs placed in the stomach the better.

Sedatives.—In mild cases, especially when the weather and other conditions make it possible to turn the patient out of doors, the use of drugs of this class is usually unnecessary, though the night will often be very disturbed unless a sedative is given at bedtime. A teaspoonful of the following mixture (4 grains each of the chloral hydrate and sodium bromide) may be given to a child of five or six if he is robust and of the average weight:

℞	Chloral hydrate	ʒj	4.0
	Sodium bromide	ʒj	4.0
	Syrup of orange to make	℥ij	60.0

Or, since belladonna seems to be of some value here (see below), the bromide may be combined with a member of that group, as in the following:

℞	Sodium bromide	ʒj	4.0
	Tincture of hyoscyamus	ʒj	4.0
	Tincture sweet orange peel to make	℥ij	60.0

Epstein (1938) used the "elixir bromaurate," which is a uniform elixir of gold tribromide; the average dosage of the elixir is a teaspoonful every four hours for children, 2 teaspoonfuls for adults. Barbiturates in combination with amidopyrine or acetanilid have also been much employed; a capsule containing sodium amytal ½ grain (0.03 Gm.) and acetanilid 2 grains (0.12 Gm.) may be prescribed and the contents of ¼ to 1 such capsule according to age (one to seven years) may be given one-half hour before bedtime in jelly, followed by a hot drink; or the dose may be given one-half hour before mealtime and at midnight if necessary. Chlorbutanol (chloretone) is said also to be useful as a sedative here. Two grains (0.13 Gm.) may be dissolved in a little whiskey, sweetened and diluted to taste, and given to a child of five or six. Older children may take it in capsules; the adult dose is 5 to 20 grains (0.32–1.3 Gm.).

In severe cases in which it is necessary to make some attempt to control the paroxysms throughout the twenty-four hours, antipyrine is much used. Practically all writers are agreed that it is worth a trial in every case. I am not able to explain the effectiveness of this very mild sedative, nor do I know of a careful study of its use with control cases. Regarding administration, Haynes and St. Lawrence wrote: "The former, antipyrine, may be used with safety in doses of 1 grain every three hours to an infant of six months. Later it

may be increased to 1 grain every two hours. At two years of age 2 grains may be given at four- to six-hour intervals, gradually increasing the frequency until 2 grains every two hours is reached. The drug is well tolerated in fairly large doses by children. Sodium bromide may be combined with the antipyrine."

Belladonna is also rather universally used. Regarding this drug, the same authors wrote: "In using belladonna it is important to begin with small doses and to exercise care in increasing their frequency and size. It is well to begin with 1/10 of a minim of the fluid extract three times a day for an infant of six months. At two years $\frac{1}{4}$ of a minim may be given every four hours, gradually increasing until it is given every two hours." It is claimed that the antipyrine or the belladonna lessens the frequency but does not reduce the violence of the paroxysms.

Ether in oil by rectum was introduced into the therapeutics of whooping cough a good many years ago by Elgood. It continues to enjoy good repute for the control of severely paroxysmal cases, the most recent favorable report I have seen being that of Musser (1941) in New Orleans. A 50–50 mixture of ether and olive oil, in a dose of 1 drachm (4 cc.) per year of apparent age, is injected into the rectum and the buttocks held together for a few minutes until there is no longer danger of the mixture being expelled.

Ephedrine and Synephrin.—Good results were reported a number of years ago with ephedrine hydrochloride: $\frac{1}{4}$ grain (0.015 Gm.) to children over one year of age, $\frac{1}{8}$ grain (0.008 Gm.) to those younger, in solution at bedtime, or night and morning, and occasionally three times daily. Some of the usual toxic symptoms are of course observed. Synephrin is used in doses of $1\frac{1}{2}$ grains (0.1 Gm.), scaled up or down for age; it is said to cause fewer side-effects than ephedrine.

Inhalants.—Occasionally a patient is benefited by the use of some such preparation for inhalation as is described in the discussion of the Common Cold; Epstein uses a teaspoonful of his elixir of gold tribromide in this way. However, these inhalants should not be used in children who are running in and out of doors during the colder months, for the mucous membrane seems to be especially susceptible to secondary infection for an hour or more after their use.

Oxygen Deprivation.—In 1942, Lauener and Maeder in Switzerland took 250 patients in the paroxysmal stage of whooping cough up in airplanes to heights of 11,000 to 12,000 feet and kept them there for about forty minutes; it was said that in about 23 per cent of the cases abrupt cure took place and that in an additional 32 per cent the paroxysms had disappeared within a day. Attempt to repeat the experiment in another study, *i.e.*, the taking of patients up to an altitude of 10,000 feet on a mountain top was unsuccessful, but results with artificially produced "flights" in low-pressure chambers were just as good as those obtained in the actual plane flights. What could bring about such remarkable effects seems still to be anybody's guess but one can look forward with much interest to further study of this matter after the conclusion of War II.

Abdominal Binder.—In 1907, Kilmer reported that general improvement, and especially a reduction in the number of vomiting spells, was noted in 95 per cent of 550 cases treated with an elastic abdominal belt. Since that time this device has come to be employed by a great many practitioners, usually employing Luttinger's modified binder (marketed by Becton, Dickinson and Company). Luttinger wrote:

"I found these bandages very serviceable in all stages of whooping cough. When applied early, they positively lessen the number of vomiting spells, and thereby contribute to better nourishment and resistance to the infection. The child is comfortable, and the older children often cry for it. They seem to feel a sense of security with it as they have 'something to cough against.' I do not think the bandage has any direct influence on the paroxysms. The improvement noticed by Kilmer was probably due to its indirect effect of promoting the general comfort and preventing vomiting. It is possible that this is due to pressure on the vagus, as it has been noticed by ocean travelers that tightening the abdomen often prevents seasickness. In view of the decided benefit from the wearing of the abdominal bandage, particularly the almost immediate disappearance of the vomiting, I strongly recommend its use in every case of pertussis."

Hyperimmune Human Serum.—McGuinness and associates (1944) have been studying such serum for several years. It is prepared from the blood of individuals who are known to have had whooping cough in childhood and who in addition have received repeated injections of pertussis vaccine. These workers found such serum of considerable value in the treatment of whooping cough. In the East, the serum is prepared at the Serum Center of the Philadelphia Children's Hospital, and Huenekens (1944) said it can be obtained in the Middle West from the University of Minnesota Serum Laboratory. The dosage is that employed in prophylaxis.

Vaccines.—Trials of therapy with vaccines of several different sorts have been going on for years, but the evidence is very conflicting and it does not seem to me that any of these methods merits description as yet.

PROPHYLAXIS

Vaccine.—In no other disease do the many variables which must be taken into account in estimating the value of prophylactic measures form so great a stumbling block for the investigator, however well-intentioned and earnest he may be, as in whooping cough. We know with certainty that the older classical forms of pertussis vaccine had no value as preventives of the disease, but the newer types of vaccine nowadays employed have certainly won more advocates than detractors. Of the recent reports which covered a sufficiently large number of injected individuals and controls, and were conducted over a long enough period, to give them perhaps as much statistical significance as can be attained in this disease, those favorable to these vaccines as decreasing the incidence in exposed contacts were the Evanston study of Sauer (1939), the San Francisco study of Miller and Faber (1939), the Grand Rapids study of Kendrick and Eldering (1939), the San Francisco study of Singer-Brooks (1940), the Chicago study of Rambar *et al.* (1941), and the study in Iceland of Dungal *et al.* (1944). Weiss and Kendrick (1943) applied a statistical method of evaluating the success of the immunization program in Grand Rapids and concluded that the proportion of cases prevented was 84 per cent. The chief unfavorable findings were those in the New York study of Siegel and Goldberger (1937) and the Cleveland study of Doull *et al.* (1939).

A report of the Committee on Therapeutic Procedures for Acute Infectious Diseases and on Biologicals of the American Academy of Pediatrics (1943) supplied the following specifications for the employment of the several vaccines: (*a*) Pertussis Vaccine Immunizing (Sauer) 6 cc. of vaccine standardized to 15 billion organisms per cubic centimeter, three injections at three-week

intervals, or (on the West Coast) 2.5 cc. of vaccine standardized to 40 billion organisms per cubic centimeter, three injections at two- to four-week intervals. (*b*) Pertussis Vaccine Immunizing (Kendrick and Eldering) 7 cc. of vaccine standardized to 10 billion organisms per cubic centimeter, four injections. The Committee recommended the use of phase I vaccine. (*c*) Pertussis detoxified antigen in dosage of 1.5 to 2.0 cc. for three to five doses every two to three days. (*d*) Alum precipitated pertussis vaccine (Harrison-Bell) 0.2, 0.3 and 0.5 cc. every four to eight weeks, standardized at 40 billion killed pertussis organisms per cubic centimeter. Most experience has been had with the Sauer and Kendrick types of vaccine, but the review of Felton and Willard, in late 1944, indicated that considerably more experience is still required before we can be certain that the superiority of any one of the vaccines currently used has been established. The injections are given first in the left deltoid region, then in the right deltoid region, and then in the left triceps region.

It is generally felt that the best time to begin the pertussis immunization is after the child has passed its sixth month, this impression resulting largely, I believe, from Sauer's (1941) finding that only 27 per cent of 89 infants developed complement-fixing antibodies following immunization with vaccine given at or below the age of three months, whereas over 70 per cent of the group inoculated at an older age showed positive complement-fixation tests; in this study also whooping cough occurred seven times more frequently among children inoculated before the third month of life than among those inoculated after the seventh month. However, I do not believe any extensive study of the earliest age at which immunity to pertussis can be acquired has been performed, at least I have seen no report of such a study, and as a matter of fact many pediatricians are now beginning their immunizations shortly after the third month because of the fact that at least half of the pertussis mortality has materialized before the infant has reached seven months.

When employing the Sauer or Kendrick vaccine mild local reactions may occur and subcutaneous nodules appear which persist for a few weeks but require no treatment. Occasionally there is a loss of appetite and rise of temperature for twenty-four hours. The Sauer vaccine is prepared from organisms grown on Bordet-Gengou medium to which only human blood has been added and it therefore cannot sensitize the patient to other serums; the Kendrick vaccine has had sheep instead of human blood added to the medium. The vaccines must be stored in a cold refrigerator at all times. Sako *et al.* (1945), employing alum-precipitated vaccine in 6600 inoculations in infants, observed sterile nondisturbing abscesses in 0.6 per cent of infants; in a subsequent study they found that if in evacuating the air from the syringe after it is filled the vaccine is not allowed to come up so high in the needle as to cover the outside of the tip these abscesses can be entirely avoided.

Mishulow *et al.* (1942) vaccinated 29 women in the third trimester of pregnancy without the production of unduly severe reactions or untoward results, and Cohen and Scadron (1943) felt that their preliminary studies indicated the possibility of immunizing the infant by such immunization of the mother during pregnancy.

Combined Whooping Cough and Diphtheria Immunization.—The recent studies of Kendrick (1943) and of Sauer *et al.* (1944) indicated that infants can be satisfactorily immunized against diphtheria and whooping cough when three doses of mixed diphtheria toxoid and pertussis vaccine are administered

Diphtheria Toxoid Alone.—Turnbull (1945) reported that in 61 children unquestionably exposed to whooping cough who were inoculated with diphtheria toxoid *alone* occurrence of whooping cough was prevented; in 4 others such prevention did not occur. I merely record Turnbull's observation here for the reason that it is extremely interesting.

Hyperimmune Human Serum.—McGuinness *et al.* (1940) used hyperimmune serum prepared by injecting adults who had had whooping cough in childhood with three courses of Sauer's vaccine, each course consisting of three weekly injections of 2, 3 and 3 cc. respectively; one month after the last course the serum was obtained and processed by the lyophile method; most of the donors continued to receive courses of vaccine and were bled at one- to two-month intervals. Ten to 20 cc. of this serum were injected intramuscularly into children upon exposure. This method of attempting passive immunization of infants after exposure to whooping cough has been reported upon very favorably; indeed, Huenekens (1944) said that from 60 to 90 per cent of children are protected and that when the disease does develop in children who have been so treated it is almost never severe.

YAWS

(*Frambesia Tropica, Pian, Bubas*)

Yaws is an infectious disease of the tropics which is acute in its onset but chronic in its course, the early manifestations being most frequently seen in children and young adults. After a noncharacteristic prodromal period of two to four weeks, there appears a skin lesion known as the "mother yaw," usually upon the site of an abrasion on a lower extremity. From one to three months after the appearance of this primary lesion, during which time the patient has generally been free of systemic symptoms, the secondary stage begins. This stage is characterized by a brief period of headache, rheumatic pains and intermittent fever, and then the appearance of the secondary crop of lesions. The eruption is quite generalized but occurs with greatest frequency on the limbs and face; there may be a ring of lesions around the anus and mouth; the scalp nearly always escapes. Characteristically a "yaw" is a nodule varying in size from a pea to a large nut and covered by a yellow or yellowish-brown crust from beneath which there exudes a thin fluid. If the crust is removed, there is revealed a raw surface whose fungoid granulations have given the name "frambesia" to the disease (*frambesia:* raspberry). Surrounding this lesion there is a dark area in natives, a reddish area in whites. The lymph glands often enlarge in groups but never become painful or suppurate. Mucous membrane lesions are very rare, perhaps they do not occur at all; but the mucocutaneous junctions are frequently involved. Occasionally there is a juxta-articular condition closely resembling acute rheumatic fever, but it does not respond to the salicylates. The lesions, which are usually itchy but never painful, disappear in three to six months in children and six to twelve months in adults, leaving behind apigmented or hyperpigmented areas. Most cases terminate at this point, but when a tertiary stage appears it is characterized by periostitis or osteitis, or by a gummatous type of nodule or ulceration, which on healing accounts for much later deformity; it is impossible to make clinical

differentiation between these lesions and those of tertiary syphilis (Pardo-Castello, 1939; Fox, 1939). Gangosa, a very destructive condition of the nose and mouth, which often before it subsides has converted the two cavities into one hideous opening in an almost featureless face, is most probably an unusual manifestation of third-stage yaws; so also possibly is goundou, a deforming exostosis of the bridge of the nose.

The causative organism, *Treponema pertenue* (Castellani, 1905), may be found in abundance within the thickened epidermis in early yaws and also, as shown by Goodpasture, within the perivascular connective tissue of the papillae. This organism can be differentiated with difficulty if at all from *T. pallidum* of syphilis, but the lesions which appear when it is inoculated experimentally in both animals and man differ clinically and histolopathologically from those of the latter disease. In addition, the primary lesion is never venereal, the central nervous system is not attacked and the cardiovascular system probably not, the disease is not congenitally acquired and an individual may have both yaws and syphilis at the same time. The Wassermann and Kahn tests are positive in yaws as in syphilis.

The opinion was formerly held that the disease may have had its original home in Africa, since epidemics frequently broke out on slave ships and the early planters in the West Indies quarantined the newly arrived slaves in an attempt to hold it in check, but according to Scott (1943), Oviedo, who accompanied Columbus, recorded meeting the disease in Hispaniola (Haiti). At the present time it does not occur indigenously in Europe, the United States, or Canada, and imported cases do not effect a spread in these lands. Indeed the occurrence of yaws in white men anywhere is extremely rare unless the three entities known in Ireland, Scotland and Scandinavia, respectively, as button-scurvy, sibbens and radesyge are accepted as yaws; Kinell's (1944) and Lofgren's (1944) reports, each of an apparently undoubted case of yaws in one of our white soldiers in the South Pacific during War II, were of extreme interest. But the disease abounds in tropical Africa and Madagascar, in southern Formosa, in the Federated Malay States, in French Indo-China and in the Netherlands Indies. It is common in southern China and in Burma, Assam and Ceylon, but is rare in India proper, particularly in the western part. It is very prevalent in the West Indies, some parts of Central America and the northern parts of South America, in the Philippines, in Australia and New Guinea and in all the mid-Pacific islands. The studies of Ramsey among the hill tribes of Assam, and of Lopez-Rizal and Sellards in the mountains of northern Luzon completely upset the previous belief that the disease is confined exclusively to lowlands, though in the highlands it does assume a somewhat different character.

To the historically inclined student, the controversy regarding the alleged identity of yaws and syphilis is of immense concern, but lack of space, together with that declining temerity which paces the marching years, forbid me to enter into the matter here. The especially interested reader will find that the published studies of the late Rear Admiral Butler (M.C.), U.S.N., and of Captain Holcomb of the same service, and those of Professor Blacklock of the School of Tropical Medicine in Liverpool, England, and the interesting treatise of Hamlin (1939) will lead him into the voluminous literature. As one entirely outside the subject I cannot refrain from remarking, however, that the demonstration by Kumm and Turner (1936), of the Jamaica Yaws Commission, of the transmission of yaws from man to rabbits by an insect vector of the

Hippelates genus, seems the most important contribution to the subject in recent times, and that should it prove possible to show that transmission commonly occurs in this way between man and man in nature, a truly epochal reorientation will have been effected in the study of the disease.

THERAPY

Neoarsphenamine or Mapharsen.—It is often stated, and I suppose quite generally believed by nonworkers in yaws, that one intravenous injection of this drug suffices to cure any case of the disease (I see no reason why mapharsen would not be equally effective but I have actually seen no record of its employment). This belief, however, accords but very poorly with the actual facts as they were developed by the excellent studies of Moss and his associates in Santo Domingo some years ago. These workers treated 1046 cases. About one half of the patients were reexamined from one to six weeks after treatment: of 362 patients given a single injection, only 19.8 per cent were cured or practically cured at this time, while of 169 given 2 injections, 51.5 per cent were cured or practically cured. The final conclusion, however, based upon another examination of 419 of the original 1046 patients, which was made nearly five years after their treatment, indicated that about 50 per cent of a miscellaneous series of yaws cases may be cured by one injection, that a second injection does not greatly raise this percentage, but that three injections very considerably increase the number of permanent clinical cures. More recent observations of others indicate that even much more prolonged treatment than this does not reduce the Wassermann reaction in more than half the cases treated intensively for three years. But Pardo-Castello (1939) said that the number and frequency of relapses and the persistently positive serological reactions inclined him to say that yaws is as difficult to cure as syphilis, and that the treatment should be, as for syphilis, early, vigorous and continuous. Kinell (1944) apparently had no illusions about quick cures for in the case of the white seaman infected during War II, and previously referred to above, he arranged for a complete course of 10 intravenous injections of neoarsphenamine and the same number of bismuth subsalicylate injections intramuscularly, at first at four-day intervals and later at weekly intervals. In this case, as is usual in yaws, healing was in progress after 2 injections and when the patient was transferred twenty-one days after starting his treatment all the lesions were healed.

Acetarsone (Stovarsol).—Pardo-Castello (1939) obtained satisfactory clinical results with this drug but of course no more effect on the serological reactions than with neoarsphenamine. He found it useful in native populations not only because it can be taken by mouth but because it is inexpensive. His course consisted of 4 grains (0.25 Gm.) daily for twenty days, 3 to 6 such courses being given with rest periods of two weeks between. Strong (1942) was of opinion that the full course of treatment with acetarsone may be more expensive than a course of injections with neoarsphenamine.

Bismuth.—Where insuperable obstacles to the use of arsenicals are encountered, bismuth may be employed instead, but Turner and Saunders (1933), of the Jamaica Yaws Commission, doubtless expressed the consensus when they said "the relapse rate for patients treated with bismuth salicylate is enormously higher than for those treated with neoarsphenamine." The use of the two drugs in supplementary fashion as in syphilis is the ideal which at present there seems little hope of attaining in most of the "native" portions

of the globe. Saunders and his associates found that under field conditions, 4, but preferably 6, weekly injections are the ideal.

Tartar Emetic and Potassium Iodide.—These two drugs are usually employed in the following formula, which is known everywhere in the tropics, especially of the eastern hemisphere, as "Castellani's Yaws Mixture":

Tartar emetic	gr. j	0.065
Potassium iodide	ʒj	4.000
Sodium salicylate	gr. x	0.650
Sodium bicarbonate	gr. xv	1.000
Water (or chloroform water) to make	℥j	32.000

This amount (1 ounce of the mixture), diluted to three or four times the volume with water, is given three times daily to adults, counting everyone over fourteen years an adult; half doses are given to children of eight to fourteen, and one third or less to younger children. Only the tartar emetic and potassium iodide are active against the causative organism, sodium salicylate being added to hasten the disappearance of the thick crusts and sodium bicarbonate in the hope of lessening the emetic properties of the mixture. This latter drug renders the preparation cloudy and inelegant, though it becomes clear when diluted with water at the time of administration. If emesis is produced, Castellani advised that the sodium bicarbonate be increased or that a small amount of an opiate be given before each dose. Europeans do not stand the full doses so well as do natives.

The mixture is given for ten to fifteen days, discontinued for a week and then given again for ten to fifteen days. The use of this formula is said to give very good results, though neoarsphenamine is preferred wherever it can be obtained.

Penicillin.—Whitehill and Austrian (1944) reported the use of this new agent in 17 cases of yaws. Eleven of the patients had never received previous therapy, 1 had been given bismuth and 5 had been treated with arsenic at some time before the administration of penicillin was begun. In every case the lesions had been progressing unfavorably and *T. pertenue* was recoverable from them. Penicill n was given in a dosage of 15,000 units intramuscularly every four hours day and night for five to six days. Darkfield studies, performed sixteen hours after commencement of treatment, revealed disappearance of the treponemata in 16 of the 17 patients; in none were they present at forty and sixty-four hours. All of the lesions were said to have shown definite evidence of healing at the end of sixteen hours and almost spectacularly rapid progress toward healing thereafter. Ulcers and granulomas several centimeters in diameter healed often within a week and all of the lesions but one were completely healed within three weeks; the one exceptional lesion was a large deep ulcer whose epithelialization was impeded by the development of a surrounding ring of fibrous tissues.

Results of a similarly spectacular nature have been recorded in several single case reports since the appearance of Whitehill and Austrian's paper and it therefore seems that penicillin has got off to a fine start in the treatment of yaws; early in 1945 the U. S. Army sent a commission to Haiti to study the effect of penicillin in the treatment and control of the disease on a large scale.

YELLOW FEVER

There are five major infectious diseases whose entire handling has been taken over quite properly by public health authorities or other specialists of great experience. These five are Asiatic cholera, leprosy, plague, trypanosomiasis and yellow fever; and since they do not nowadays raise problems in treatment for the general practitioner, I shall no longer allot space to a consideration of them in this book.

FLUKE INFESTATIONS

INTESTINAL FLUKES

Man is infested by a rather large number of intestinal flukes throughout a wide territory in the Far East: Japan, Korea, China, Indo-China, Thailand, India, British Malaya (Simmons *et al.*, 1944, said that most of the cases in the Settlements were imported), Netherlands Indies, the Philippines and some of the smaller Southwest Pacific Islands. Through much of this territory the chief of the flukes is *Fasciolopsis buski*, which gives rise to a syndrome of diarrhea, anemia and edema in a very small proportion of the individuals who harbor it. Those who have studied the disease are agreed that death, when it occurs, is apparently due to exhaustion. The vicious circle responsible for the perpetuation of the malady is as follows: (*a*) the use of human excrement containing eggs for fertilizer; (*b*) the hatching of the eggs in the water and their penetration into the body of certain snails wherein they pass a portion of their life cycle; (*c*) eruption of metamorphosed forms from the snail and their encystment on aquatic plants; (*d*) the eating raw of contaminated water nuts; (*e*) maturation of the fluke in the human intestine where it sows its eggs.

THERAPY

Under proper anthelmintic treatment dead flukes appear in the stools within twelve hours. Thymol, betanaphthol, carbon tetrachloride and hexylresorcinol have all been used successfully (for details of their employment see the section on Worms). Carbon tetrachloride was formerly the most used of these agents, but McCoy and Chu (1937) reported the treatment of a large number of cases with hexylresorcinol, and Faust (1939) felt that possibly tetrachlorethylene would prove to be satisfactory.

LIVER FLUKES

Liver flukes are common parasites in sheep, cattle, pigs, dogs and cats. The human cases harboring *Clonorchis sinensis* have about the same geographic distribution as that of the intestinal fluke cases, though Simmons *et al.* (1944) said that such infestations have never been reported from the Netherlands Indies. In recent years also numerous investigators have been uncovering infestations with *Fasciola hepatica* widely scattered throughout the world. *C. sinensis* passes a portion of its life in the body of a small snail and later penetrates into a certain species of small fish in whose muscles it becomes encysted; when this fish is eaten raw the parasite is introduced into the intestinal tract of man and the other animals which harbor it, whence its eggs finally issue to complete the vicious circle. *F. hepatica* gains access to the human intestinal tract when contaminated water or vegetables or salad greens are ingested. It seems possible for the majority of individuals to remain apparently healthy,

though the bile ducts, and occasionally even the pancreas and duodenum, are considerably infested with these flukes. In 367 consecutive autopsies on adult Chinese in Hong Kong, Uttley (1935) found clonorchis present in 52 instances, but in no case had the fluke been the cause of death. When symptoms arise they are the following: gastro-intestinal pain and tenderness, nosebleed, jaundice and bloody diarrhea; in severe cases edema, ascites, anemia and death from cachexia.

THERAPY

The anthelmintic drugs have been usually considered a complete failure in the treatment of liver flukes, but Kouri and Valverdi (1935) reported the successful use of emetine in 2 cases (see methods of employing this drug in Amebic Dysentery). Shattuck (1924) used tartar emetic (as in kala-azar) and the arsphenamines in 6 asymptomatic cases, and wrote: "The facts seem to indicate, first, that both tartar emetic and arsphenamines are somewhat poisonous to clonorchis; and second, that it may be advantageous to give them in successive courses"; Kinngasa (1939) found fuadin (see Bilharziasis below) superior. Faust (1939) said that gentian violet, crystal violet, or methyl violet may be helpful; oral dosage in enteric-coated pills is 30 mg. every other day and not to exceed a total of 300 mg./Kg. Manson-Bahr (1940) said that spectacular results sometimes follow duodenal tube bile drainage, a practice which seems to be widespread in Korea.

LUNG FLUKES

The fluke, *Paragonimus westermanii*, infests dogs, cats, pigs, rodents and the larger carnivorous animals over a wide range. It is also established as a human parasite throughout a wide territory in the Far East, in Central Africa, Peru and Venezuela; Faust (1939) said that reports of autochthonous cases in Mexico are apparently erroneous. Likewise, no truly autochthonous cases have occurred in the United States, though animals are infested with the closely related species, *P. hellicotti*, throughout a wide territory in our country; according to Ameel (1934), the usual mammalian host here is the mink. The fluke passes a part of its life cycle in the body of a snail and finally is taken up by a fresh-water crab and crayfish. When these mollusks or crustaceans are eaten uncooked, or the water in which they have disintegrated is swallowed, the metacercarian form of the fluke works its way through the tissues intervening between the intestinal tract and the lungs, in which latter organ it forms a cyst in which it undergoes full development. Not infrequently other organs or tissues, even the brain, are invaded. The pulmonary type of invasion is characterized by cough, frequent hemoptysis and signs of cavity. The eggs are present in the sputum or feces.

Miller and Wilbur (1944), reporting 3 cases of lung fluke infestation in individuals who have returned to the United States from the South Pacific during War II, felt that after the close of the war and the return of our soldiers and sailors it will be wise to suspect this infestation in patients who present symptoms of an unexplained chronic pulmonary disease with slight fever, cough, expectoration of brownish-yellow tenacious sputum often containing blood, particularly if these symptoms are accompanied by a history of thrombophlebitis of the leg.

THERAPY

So far as I am aware no satisfactory treatment has been developed for this malady. To and Ko (1935) reported the partially successful use, in 4 cases, of 5 per cent carpaine hydrochloride in normal saline, injecting subcutaneously. The total quantities used were respectively 0.3 Gm. over six days; 1.1 Gm. over twenty-three days; 0.5 Gm. over ten days; and 0.9 Gm. over thirty days. Emetine is also used as in amebic dysentery (*q.v.*). Bercovitz (1937) reported some relief following the bronchial instillation of lipiodol in a small number of pulmonary cases. Miller and Wilbur used emetine, sulfadiazine, phenothiazine and lipiodal injections into the bronchial tree in their cases, but they were not impressed by the results obtained.

BLOOD FLUKES

(*Bilharziasis, Schistosomiasis*)

The disease which bears the name of Bilharz, who first wrote of it in 1852, is caused by four flukes, *Schistosoma haematobium*, *S. mansoni*, *S. japonicum* and *S. bovis*. The cycle of events is as follows: the eggs are discharged in the urine and the feces of infested men or animals; in fresh water, motile larvae develop and enter certain specific snails; after about six weeks another form of larvae leave the snails and move about very actively in the water; it is these latter larvae that pierce the skin or buccal mucous membrane of persons or animals during bathing or drinking, and set up the disease. The venous system is quickly entered and in the larger portal vessels the flukes mature and become paired. In pairs (male and female) they then travel toward the periphery and become lodged in the submucosal veins of the intestines and bladder, where they deposit enormous numbers of eggs; more rarely the cerebral cortex, lungs and genital organs, especially the last, are selected as sites for these flukey nuptial couches. The pathologic reactions consist in a cellular response to the general toxemia and a local inflammatory reaction to the presence of the aggregations of eggs; chronic inflammatory changes lead ultimately to fibrosis, especially in the liver and colon; according to Koppish (1943) there is usually present but little evidence of acute colitis in the late stage. Bercovitz *et al.* (1944) described an interesting group of young Puerto Rican patients who were infected with the parasite and in whom there were definite pathologic findings in the rectal mucosa but no other clinical symptoms; in a later report (1945) on this group it was said that the blood picture was not observed to be significantly altered from the normal.

When the larvae penetrate the skin there is for a short time an intense pruritus and erythema; then, after what may be termed an incubation period of three weeks to six weeks, the toxic symptoms appear: malaise, headache, cough, chills and irregular fever, urticaria, eosinophilia, and possibly abdominal pain and tenderness localizing over the liver region. This syndrome, which is known in Japan and Egypt as Katayama disease, according to Gelfand and Osburn (1943), is not recognized elsewhere in the world as often as it should be. The symptoms due to the local processes in the bladder and intestine usually do not appear until another three to thirty months have elapsed. In the intestinal cases the symptoms are not clear cut but there are usually

recurrent attacks of bloody dysentery and colicky pain and tenesmus; there are palpable papillomata of the rectum and distinctive signs upon sigmoidoscopic examination. In bladder cases there is burning and frequent micturition, suprapubic aching, hematuria and urethral bleeding, and perhaps in later cases symptoms of cystitis and vesical calculus; tubercles and papillomata are found upon cystoscopic examination. There is a tendency for malignant growths to engraft themselves upon these local lesions. Cardiovascular and pulmonary involvement in bilharziasis has been described (Clark and Graef, 1935; Shaw and Ghareeb, 1938). Laboratory tests are of great assistance in the diagnosis: marked eosinophilia, the presence of ova in the stools and urine and in sectioned tissue from the bladder and rectum, and the complement deviation test of Fairley. Culbertson and Rose (1942) described an intradermal skin test which seemed very simple and was successful in their small series of patients, and Davis (1942) wrote of a characteristic facies helpful in diagnosis.

S. haematobium causes the bladder type of bilharziasis. It prevails in Egypt to an enormous extent and is apparently endemic throughout much of the rest of the African continent, as well as in Portugal, Spain, Greece, Cyprus, Palestine, Syria, Iraq, Iran, Arabia, western Australia, Madagascar and the two neighboring islands of Reunion and Mauritius. It seems that the proper snail host is not present in India and the Malay Archipelago, thus accounting for the freedom of these pestilential regions from at least one of the more dire maladies. Experiments a few years ago in Corsica, which was still free from infestation prior to the outbreak of War II, showed the ease with which colonial African soldiers coming from regions in which the disease is endemic may infect the mollusks in that island. *S. mansoni* occurs quite generally in Africa, cases in Egypt, for instance, being often mixed, *i.e.*, caused by infestation with both *S. haematobium* and *S. mansoni*. *S. mansoni* occurs alone also in Brazil, Venezuela and Dutch Guiana in South America, and in Antigua, Guadeloupe, Martinique, St. Kitts, St. Lucia, Nevis, Vieques, Montserrat and Puerto Rico in the West Indies. *S. japonicum* occurs to a very considerable extent in rice-growing districts in Japan and in the Yangtze Valley in China, in Korea, in scattered foci along the coast and also inland in southern China, in Formosa and in the Philippines and the Celebes. I believe the only reported cases of human infestation with *S. bovis* have been in Natal, Southern Rhodesia and in the Belgian Congo.

Spontaneous cure is undoubtedly effected in some cases of bilharziasis after a variable length of time, and it is often stated that ova cease to be passed in the urine and feces of an individual after three years of residence outside an endemic center. However, in Cutler's review of the subject a number of years ago it was clearly shown that both clinical and laboratory evidences of the disease may persist for ten or more years of consecutive residence in a non-bilharzial country. Up to the early months of 1945 I have seen reports of only 35 imported cases which have been recognized in North America; after the conclusion of War II this number will doubtless be considerably augmented, but the disease is not likely to be perpetuated here since the requisite species of snail is not found in our country.

THERAPY

Tartar Emetic.—It is only since 1918, when Christopherson introduced the use of tartar emetic, that we have been able to speak of having a specific remedial agent in this disease. Subsequent reports have all been in agreement

that the drug is remarkably effective. The most recent authoritative statistical report is that of Khalil (1935), whose percentage of cures in 1000 consecutive patients completing the course of 14 to 17 injections was 89.4. A few days after beginning treatment general clinical improvement begins and the number of ova in the urine or feces is considerably decreased. At the end of the first week there is an increase in the number of ova but many of them appear granular and black, and after two weeks half of them are obviously dead; at the end of the third week all are usually dead. Christopherson admitted that granular ova are passed in cases not undergoing treatment but pointed out that the number is never so large as in the treated cases. He believed that tartar emetic kills the ova as well as the embedded flukes. If treatment has not been entirely successful, reexamination will show ova within a month or six weeks, whereas if reinfestation has taken place, the ova will not reappear until three or four months have elapsed. Tartar emetic is given intravenously, ½ grain (0.032 Gm.) being dissolved in 6 cc. of sterile physiologic salt solution. Injections are given every second day and are increased by ½ grain (0.032 Gm.) on each occasion, though it is considered advisable to give no more than 2½ grains (0.16 Gm.) at any one time; indeed, many patients will show signs of intolerance on much smaller doses than this (see Kala-azar for symptoms of tartar emetic intoxication). A total of 25 to 30 grains (1.63–2 Gm.) for the adult, perhaps no more than 10 grains (0.6 Gm.) for children, is needed for complete eradication of *S. haematobium* and *S. japonica;* Manson-Bahr (1940) believed that much more than this is required in *S. mansoni* cases.

Fuadin.—This drug, which is one of the newer antimonial preparations, has been in use since 1929. Khalil and his associates early reported more rapid "cures" than with tartar emetic. The treatment consists of 9 to 13 intramuscular injections beginning with 1.5 cc. of the commercial solution and increasing, in injections every two days, to 5 cc. at the third injection and finishing the course at that dosage. In the most recently reported (1935) series of 3302 cases, 63.4 per cent were cured after 9 injections, 78.6 per cent after 11 injections and 83 per cent after 13 injections. The great advantages of the drug over tartar emetic are that it is given intramuscularly and causes very little pain at the time of injection or later. The alleged superiority in the matter of relative freedom from toxicity is still matter for debate. Khalil is studying a method of detecting the patient who is hypersensitive to the antimonials before treatment has progressed very far, but Diamantis (1938) considered the test impractical so far.

Acriflavine.—Fisher (1934) reported a certain amount of success with this drug given by mouth, but subsequent reports (Khalil and Salah, 1934; Fakhry, 1934) failed to substantiate his findings, though it may be that a satisfactory dosage will still be developed.

Emetine.—Tsykalas, in 1933, celebrated his introduction of this drug into the therapy of bilharziasis twenty years earlier by publishing his notes on 3800 cases. The dosage, he stated, should be 1.12 Gm., in all, given intravenously in 10 injections during two weeks; the first 4 injections of 0.1, 0.12, 0.14 and 0.16 Gm., and the remainder, 0.1 Gm. The dangers and precautions, contraindications, and so on, with regard to emetine are discussed under Amebic Dysentery. I am unable to find that anyone agrees with Tsykalas that emetine is superior to other drugs, though all observers readily admit its greater toxicity.

PROPHYLAXIS

The best method of preventing the occurrence of schistosomiasis would be to eradicate the disease in all infested men and animals by the proper employment of the "specific" drugs, but this is of course a practical impossibility. The next choice among prophylactic measures is to seek the destruction of the snail which serves as intermediate host. Sufficient advances have been already made in this direction to show that it is a practicable means of fighting the disease in some regions, but in other infested areas there are immense obstacles to be overcome before success can be hoped for. The subject is an extremely interesting and important one, but as it involves principally large-scale projects in sanitation, a discussion of it would probably be out of place here.

Of course no drinking of, or wading or bathing in, fresh water in areas of bilharzial endemicity should be indulged in. Suspected drinking water may be rendered safe for use by storing it in snail-free tanks for forty-eight hours or more, for most of the larvae perish unless they enter the human host within twenty-four hours after they leave the snail and all of them are dead at the end of forty-eight hours. Sandbed filtration is not effective against them but Berkefeld and Pasteur-Chamberland filters hold them back. The ordinary chlorination of drinking water does *not* destroy schistosoma larvae. Water for washing and bathing purposes may be rendered safe (according to Leiper) by the addition of cresol in the proportions of 1:10,000.

SCHISTOSOME DERMATITIS

("*Swimmer's Itch*")

Waders, bathers and swimmers in the lakes of the north-central part of the United States frequently complain of a severe form of itching which attacks them after leaving the water. In some of the worst years the summer tourist trade has been considerably affected by this "swimmer's itch." A similar disturbance troubles swimmers in Great Britain and on the Continent also. Not every person in a bathing party is affected, though the exceptions are in the minority; children are the most frequent and most severe victims. In a typical case the itch is fully developed in half to one hour after leaving the water and is followed in a few hours by a scattered pin-point macular and then papular rash. When the lesions are mature they much resemble chigger bites and of course may become secondarily infected from scratching. The itching frequently increases greatly at night but ordinarily disappears in about three days, the lesions often requiring several weeks to fade out. In 1928, Cort, of Johns Hopkins University, determined this malady to be due to penetration of the skin by the free-swimming larval forms of certain schistosomes; Cort subsequently contributed much to further the understanding of the subject, and in more recent years Brackett and his associates considerably added to our knowledge. Of a number of schistosomes which are known to be the active agents in this country, it seems that *Cercaria stagnicolae* is the principal offender. What happens is this: the eggs of this fluke are dropped into the water in the feces of some animal unknown (but considered most likely to be one or more migratory birds); they develop into embryos which enter the bodies of snails; after awhile in the snails a free swimming larval form emerges (the

cercariae) and goes about in the water searching its natural host, the birds, having entered and penetrated into the blood vessels of which, they make their way into the intestinal veins so that the eggs may be deposited in the water as above described; but if a human being is in the water and in the path of these cercariae they strive to enter his body, their presence in the skin giving rise to the itching and the visible lesions. Brackett's (1940) histologic studies showed that the organisms are destroyed in the epithelial layers of the skin and probably do not reach the deeper tissues, so there is no warrant in present knowledge for the fear that a systemic form of schistosomal infection will result from one of these attacks.

THERAPY

Ridding lakes and bathing beaches of snails by the use of copper sulfate or carbonate or formaldehyde additions to the water has not proved an entirely practicable measure as yet. Brackett (1939) showed that the best protection against an attack is to rub down the body vigorously with a towel after leaving the water—not soon after leaving but at once, for there is evidence that most of the penetration takes place when evaporation begins; for this reason children who are paddling in and out of the water frequently are the most severely affected.

Antipruritic lotions (see Index) are usually the only agents indicated in treatment.

WORM INFESTATIONS

TAPEWORMS

The principal tapeworms infesting man are *Taenia saginata*, *T. solium*, *Hymenolepis nana* and *Diphyllobothrium latum* (*Bothriocephalus latus*). The following have also been occasionally recorded: *Hymenolepis diminuta*, *H. lanceolata*, *Diphyllobothrium cordatum*, *Diphyllobothrium ranarum*, *Dipylidium caninum*, *Diplogonoporus grandis*, and *Davainea madagascariensis*. In 1942, Chandler described the first recognized infestation of man with *Mesocestoides variabilis*.

Taenia saginata, the beef tapeworm, occurs all over the world wherever beef is eaten; it and *Hymenolepis nana* are the two most common tapeworms in the United States and Canada. It attaches itself in the upper part of the intestinal tract of man only, usually but one worm being present at a time. The larvae encyst in the muscular tissues of cattle, and it is the eating of these tissues raw or insufficiently cooked that introduces the parasite into its human host. If beef is solidly frozen the larvae die within six days and they die also in ordinary cold storage of three weeks' duration, but in the latter case their death is due not to the low temperature but to the fact that they are unable to survive the death of their host for a longer period.

Hymenolepis nana, the dwarf tapeworm, is quite common throughout the world though it particularly favors the warmer climates; in the Western Hemisphere it shares the honors with the beef tapeworm. It is acquired by the direct swallowing of the ova from an infested individual and is especially frequent in children. There is some presumptive evidence that the rat flea may act as intermediate host by harboring the larval stage of the worm.

Taenia solium, the pork tapeworm, on the whole infests man much less frequently than the beef tapeworm but is rather common in parts of South America, India, Egypt and Malaya, and also occurs in somewhat circumscribed areas elsewhere in both hemispheres; in North America it is of very infrequent occurrence. The larvae are encysted in the tissues of pigs and pass into the human intestinal tract when this "measly" pork is eaten raw or insufficiently cooked. Infested pork is not rendered safe for human consumption by cold storage or even by freezing. The larvae are also harbored in deer, bears, monkeys, dogs and cats. Man can become infested with the larvae by eating foods contaminated by another infested individual, as it does not seem necessary for the larval stage to be passed in another animal; he may also reinfest himself if a ripe proglottis happens to pass upward into the stomach, where it will liberate its ova. The larval form, *Cysticercus cellulosae*, sometimes enters the blood stream and, becoming encysted in the tissues, gives rise to the entity known as "cysticercosis" with a variegated array of symptoms; death of such encysted larvae in the brain, followed by the liberation of the toxic products of their dissolution may give rise to symptoms indistinguishable from those of idiopathic epilepsy. The adult worm develops only in the intestinal tract. Multiplicity of worms is not the rule but the occurrence of more than one is more frequent than with the beef tapeworm.

Diphyllobothrium latum, the broad or fish tapeworm, is common in Japan, Turkestan, Roumania, Poland, Switzerland, many parts of Africa, and particularly in the countries bordering upon the Baltic Sea. The eggs of this tapeworm hatch in water and the larvae enter the bodies of certain small crustaceans; fish are infested by swallowing the crustaceans and man by swallowing the fish uncooked. Neither smoking nor salting will destroy the larvae; only thorough cooking will do it. The adult worms develop in large numbers in the intestinal tract of man, dogs, pigs, cats, foxes and perhaps all other fish-eating animals; they are very long-lived, a case being on record in which one of these worms was harbored for sixteen years. It is therefore not remarkable that the western portion of the Great Lakes region of the United States and Canada, so largely populated by immigrants from the Baltic region, has finally come to be recognized as an endemic focus for the dissemination of the larvae of this worm. Warthin, in 1897, warned that this might be expected, and his later observations and those of Vergeer proved how true was the prediction. At least four species of food fishes have been inculpated. It seems that these are taken commercially in only very small amounts from the contaminated portion of Lake Superior, but Vergeer believed that infestation would spread through the shipping east, for the Jewish trade, of large amounts of fresh fish from Lake Winnipeg, Lake Manitoba, Lake of the Woods and Lake Winnepegosis; subsequent observations have shown that human infestation is increasing in the eastern portions of the United States and Canada. Essex (1938) found that in a small lake in Minnesota the level of infestation of the fish remained about what it had been in 1930. In 1943, Summers and Weinstein reported 3 cases of *Diphyllobothrium latum* infestation in Negro children in subtropical Florida; these cases were thought to have been almost indubitably acquired through the eating of improperly cooked fish native to that region.

Tapeworm infestation is said to be manifested by any or all of the following symptoms: abnormal appetite, picking of the nose and scratching of the anus, restlessness at night and a large array of nervous symptoms by day, vertigo and a sinking sensation, anemia, a sensation of weight in the epigastrium, attacks of colicky abdominal pain, nausea and vomiting, and ova in the stools. The ova can always be found if the microscopist is an expert and is not satisfied with a single examination. In the case of *Taenia saginata*, segments often wander out of the anus when the patient is not at stool so that he soon becomes aware of his malady; segments of the other members of the group are usually passed unnoticed with the feces. In individuals harboring *Diphyllobothrium latum*, the blood picture sometimes closely resembles that of pernicious anemia, but Mackie (1942), in the United States, said that there is no direct association between the presence of this worm and macrocytic anemia; however, von Bonsdorff in Finland, where great numbers of these cases are seen, was still very closely studying the matter before War II involved his country and when he last reported, in 1940, seemed still of the belief that such anemias are at times caused by the worms. It cannot be too strongly impressed upon the reader that his patient may harbor any of the tapeworms and manifest no symptoms whatever. To examine the stools of any individual whose symptoms are of a vague nature is good practice.

THERAPY

In the treatment of a patient infested with any of the tapeworms several things are essential to success. In the first place, the intestinal tract must be

thoroughly cleaned out in order that the vermifuge may have free access to the parasite. The work of Macht and Finesilver showed that magnesium sulfate is the best cathartic to employ for this purpose since for several hours after its use the absorption of all other drugs is much retarded. Second, the dose of the vermifuge must be large enough to stun the worm only, for a dose large enough to kill him is somewhat dangerous to the patient. Death following the use of these vermifuges is rare, but great depression and even collapse are not infrequent; therefore the patient should be caused to stay quietly in bed throughout the course of the treatment. Third, the dose of the drug must be followed by another saline purge in order to sweep out the worm and the remnants of the drug. Fourth, careful search must be made for the head. If the treatment has been successful it will nearly always be found *if properly searched for by the physician himself*, though it sometimes is discharged separately within the next few days, or it may be digested and not discharged at all; the latter occurrence is probably very rare. In any case, if ova continue to be passed in indication that the treatment has failed, it should not be repeated in less than one month and in weakly individuals not for a much longer time.

The toxicology of vermifuges is presented at the end of this section. It is probably well not to employ any of these drugs during pregnancy—pumpkin seeds are the exception as these seem to be harmless under any conditions.

Aspidium (*Male Fern*).—The usual dose of the oleoresin of aspidium as gauged for children is 0.5 Gm. per year of age, but not to exceed 5 Gm. Indeed, even in an adult it is doubtfully advisable much to exceed this latter dose. The substance is extremely disagreeable in taste and is difficult to disguise. The following prescription, which is for a child of five, is about as satisfactory as any.

℞	Oleoresin of aspidium	gr. xl	2.6
	Fluidextract of glycyrrhiza	ʒiiss	10.0
	Syrup of orange flowers	ʒv	20.0
	Peppermint water to make	℥ij	60.0
	Label: To be taken in 1 dose.		

Magath and Brown, of the Mayo Clinic, use the following emulsion for an adult:

℞	Oleoresin of aspidium	ʒiss	6.0
	Powdered acacia	ʒij	8.0
	Water to make	℥ij	60.0

They direct that the patient should omit luncheon and supper on the day preceding treatment, though black coffee, tea and water are allowed. At 6 P.M. a dose of magnesium sulfate is taken and this is repeated at 6 A.M. next day. Then, without breakfast and after the bowels have moved, half the dose of the drug is given; one hour later, the other half. After two more hours, another dose of magnesium sulfate, and two hours after this a large soapsuds enema. The stool is then passed into a container, but the toilet paper should be separately disposed of. In searching for the worm head, the top half of the stool is poured off and the rest poured through a 20-mesh sieve, followed by warm water, so that the sieve will contain only the worm. The worm is then rinsed out into a pan with black-painted bottom to facilitate search for the head.

It is now no longer held to be true, according to Travell (1939), that castor oil increases the toxicity of aspidium.

All of the other vermifuges are used, of course, to eliminate the tapeworm, but I believe that none is as often effective as aspidium. The following are those with perhaps the best record.

Pumpkin Seeds (Pepo).—Pumpkin seeds not over a year old, and the fresher the better, have definite anthelmintic value. Thirty to 50 Gm., according to the age of the individual, have been considered the standard dose in the past, but Krayer (1937) said that doses much larger (he used up to 200 Gm. for an adult) must be used in order to obtain best results; in short there is apparently no harm in giving all the patient will accept. The seeds are reduced to a paste in a mortar and rubbed up with sugar and perhaps a little honey. It is said that children like this mixture, to which a little milk may be added if desired.

Pomegranate Bark (Granatum).—From 50 to 60 Gm. of fresh bark are thoroughly bruised in 750 cc. of water and allowed to stand for twelve hours; this is then boiled to about 500 cc., cooled, a little syrup added, and administered. This is an effective remedy but one which is nearly always vomited. Half this dose is sufficient for children.

Pelletierine Tannate.—This is a mixture of several alkaloids of the above bark and is easier to give since the dose is small, being only 4 grains (0.25 Gm.) and it can be easily suspended in simple syrup. This is considered by many practitioners to be the most surely effective of all the vermifuges available for the treatment of tapeworm, but it is too toxic for any but very robust individuals and it should perhaps never be given to children.

Carbon Tetrachloride.—Sandground (1938) reported the successful use of this drug in a small series of cases (see methods in Hookworm), and Mackie (1939) and Mukerji and Maplestone (1943) also commended it; there have been earlier favorable reports but the drug has not been widely adopted for use in tapeworm infestation.

"Early Bird."—This concoction, still employed in some hospitals, is prepared as follows:

Pumpkin seed	8 Gm.
Cusso	4 "
Pomegranate	4 "

Make an infusion, to which is to be added:

Kamala	4 Gm.
Oleoresin of aspidium	4 "
Glycerin	15 cc.
Mucilage of acacia	15 "
Water to make	240 "

This quantity is taken in two drafts two hours apart, after the usual preliminary treatment. Bastedo says: "The 'early bird' usually gets the worm," but he has several times seen severe gastro-intestinal irritation with vertigo and prostration result from the use of this mixture.

Tetrachlorethylene.—Dutt (1942) reported the satisfactory employment of this agent in 3 cases (see methods in Hookworm).

Transduodenal Treatment.—Sokolovski (1933) reported success in promoting expulsion of the worm and head in thirty to sixty minutes in 10 of 11 cases in which he administered 15 grains (1 Gm.) of quinine (the salt used was not stated) in 10 per cent alcoholic solution by duodenal tube; the quinine was followed down the tube in five minutes by 15 cc. of 25 per cent magnesium

sulfate solution. Golob (1935) administered aspidium emulsion simultaneously with 30 cc. of saturated solution of magnesium sulfate by the tube in a single case; the mixture was vomited despite the fact that the tip of the tube lay in the second portion of the duodenum but the vomitus was saved, kept warm, and later reintroduced with the addition of more magnesium sulfate solution. The worm was expelled with head intact. Clements (1935) reported a very recalcitrant case in which he felt justified in performing an appendicostomy, inserting a catheter, and flushing the intestine out with 1 per cent solution of iodine; the head of the worm came away within five minutes and the patient recovered and remained free of symptoms of infestation.

HYDATID DISEASE

(*Echinococcus Disease*)

Taenia echinococcus is a small tapeworm of the dog and his congeners, the fox, the jackal, the wolf, etc.; more rarely it infests other carnivorous animals. The ova are spread in the feces of the infested dog and are also deposited upon the objects which he licks with his tongue. Grass-eating animals such as cattle, sheep, pigs, deer, moose (but not, according to Barnett, 1939, the rabbit) take up the ova with their food and act as secondary hosts for the parasite; when the dog eats the uncooked viscera of these animals he acquires the larval form of the worm, and so the vicious circle is perpetuated. Man may acquire the ova by too intimate association with infested dogs, or much more rarely by ingesting uncooked contaminated vegetables or drinking water. The embryo is freed by the digestive juices in the stomach, passes down the intestine, is taken up by the portal vein and passes to the internal organs, where the larvae in developing cause the condition known as echinococcus disease. The liver is the stopping place for the parasite in about 75 per cent of the cases, the lung in about 9 per cent and all the other organs and tissues combined in about 16 per cent.

Since a pathologic description of a hydatid cyst is not within the province of this book, it must suffice here to say that the ultimate form of this cyst is a brood capsule which contains, if not secondarily infected, a crystal-clear fluid and a great many scolices or rudimentary worm heads; there are usually quite similar cysts within the cavity of this primary cyst, and even these secondary cysts may themselves contain cysts. The symptoms are those of a characteristic tumor in an individual not otherwise greatly affected in health. X-ray, the complement deviation and the intradermal tests are of great assistance in making the diagnosis, though none of these tests seems to be infallible. Of course if rupture takes place into any of the body cavities, the symptoms of shock and collapse are to be expected. After such a rupture a new crop of cysts may develop in great number. If a cyst becomes infected, which often takes place through the bile ducts apparently, the picture of sepsis plus jaundice and often urticaria is superimposed. In regions where the disease is frequently encountered it is not often confused with other entities, such as malignancy or tuberculosis, but where hydatid disease is unusual the diagnosis is rarely made outside the operating or autopsy room.

At the present time echinococcus disease is most prevalent in Australia,

New Zealand, the Argentine, Chile, Uruguay, Cape Colony, southern Brazil, Mecklenburg, Pomerania, Bavaria, Switzerland, Iraq, Iran, Austria, Jugoslavia, Hungary, Dalmatia, Bulgaria, Greece, Turkey, Egypt, Russia, Siberia, Morocco, Palestine, Syria, Roumania, France, Italy, Wales and Iceland. For most of the world there are no reliable figures available. Maplestone (1933) believed that the incidence is higher in India than the literature would indicate. Hinshaw (1937) stated that in Syria the disease is one and one half to three times as common as in Australia and New Zealand, four times as common as in Egypt and ten times as common as in Iceland. Magath (1937) said that at least 482 cases had been recorded in Canada and the United States since the first case seen in 1808; of these patients only 3 had likely acquired the infection in Canada and 19 in the United States; in 1938, Sawitz reported another autochthonous case in the United States, and in 1944, Worthen and Jenovese, and Holman and Pierson, one case each.

THERAPY

I am unable to find any satisfactory evidence that either drugs or biologicals are of the least value in the treatment of hydatid disease. Direct surgical attack, on the other hand, is often productive of the most excellent results. Theoretically, the use of the x-ray would be indicated, but the work of Deve conclusively showed that its employment is impractical for the reason that the scolices within the cysts succumb only to a dose of the ray which would be highly injurious to the tissues of the patient.

PROPHYLAXIS

In Iceland, which has been a great sheep-raising country for over a thousand years, hydatid disease reached its highest incidence about 1867, since which time a remarkable drop has occurred. Ofeigsson (1937) listed the following prophylactic measures as having effected this change: (1) the decrease in poverty with increased freedom from foreign rule and especially since Iceland became a free country; (2) better hygiene; (3) Krabbe's discovery in 1863 of the life cycle of the echinococcus; (4) the rapid spread of the knowledge of this discovery among Icelandic doctors and laymen, who realized the importance of breaking the life cycle of the parasite; (5) more and better doctors; (6) laws forbidding all unnecessary dogs, resulting in a great reduction of their number; (7) a quarantine for two days, once or twice a year, of all dogs during which they are treated with baths and suitable drugs; (8) warnings to people against too much petting of their dogs and careful washing of their hands after touching them; (9) laws forbidding farmers to slaughter their sheep on their farms and permitting only authorized slaughter houses which are supervised rigidly; (10) inspection of all meat by veterinary surgeons; and (11) burning or burying of all infected organs of sheep and cattle. According to Barnett, in 1941, in spite of a similarly intensive preventive campaign the incidence of infection had not yet begun to wane in New Zealand.

Turner (1933) and associates reported the artificial immunization of dogs with some success through injecting an antigen obtained from cysts; Penfold (1938) failed in an attempt to immunize lambs.

THE COMMON ROUNDWORM

Ascaris lumbricoides is the intestinal worm most commonly infesting man. It is quite ubiquitous, but in cool climates is encountered principally in children. In the tropics, however, and in many regions of poor sanitation in northern latitudes, the incidence is very much higher and the worm occurs in individuals of all ages. In China, and other countries where the Chinese custom of employing night-soil in vegetable gardens prevails, it is also harbored with a frequency which is astonishing to practitioners in Europe and North America; in Egypt, about 6 million of the 15 million people harbor this worm, average prevalence in the Nile delta itself being as high as 80 per cent according to Scott (1939); Fernando and Balasingham (1943) estimated that two thirds of the population of Ceylon are infested.

This parasite needs no intermediate host for its full development. When the egg is swallowed by man it hatches in the small intestine, migrates to the liver and then to the lungs; from the latter situation it passes up the trachea and down the esophagus and through the stomach to settle down to maturity in the small intestine. An individual usually harbors from four to six of the adult parasites but sometimes the number is much greater than this. Any, many, or no symptoms may herald the presence of roundworm; the infestation is most often diagnosed by suspecting its presence, *i.e.*, searching for the ova in *several* stools. When an individual harboring roundworms develops fever, as during the course of one of the infectious diseases, the worms seem to be disturbed and show some tendency to wander from the intestine into the stomach, esophagus, upper air passages, bile ducts, or even more distant parts of the body. Remote wanderings are very rare, however. Christie found only 10 instances of migration in a study of 800 postmortem reports of roundworm cases. Their liability to complicate laparotomy cases is of more importance and should be taken into account in all regions of heavy infestation. Ludlow's experience in Korea indicated the advisability in regions of heavy infestation of routine anthelmintic treatment prior to surgical procedures in all cases in which it is not definitely contraindicated.

THERAPY

Hexylresorcinol.—As a result of the studies of Lawson and his associates, in 1931–1932, this drug has come to be the preferred one on the basis of relative nontoxicity; with regard to efficacy, Smillie (1942) said that a single administration will remove about 80 per cent of the worms. It is used in the following dosage: 6 grains (0.4 Gm.) to very young children; 10 to 12 grains (0.6 to 0.8 Gm.) to those from six to twelve years; 15 grains (1.0 Gm.) above twelve years. The best method is to give the drug early in the morning on an empty stomach, followed within an hour to an hour and a half by a saline cathartic, and then no food to be taken until noon. Often there have been complaints of slight burning gastric irritation and occasionally a patient vomits, but no reactions of more serious moment have been recorded. The drug was first made available in crystalline form in hard gelatin capsules but it was said that a reaction often occurred between the active agent and the gelatin (particularly in warm, moist climates); an occasional superficial burn of the mucosa of the mouth was also seen if children chewed the capsules. The first substitute for these capsules was the familiar sugar-coated pill, but as this can also be chewed a new form has now been found, an "iron-bound" capsule which is said to be impossible to chew.

Oil of Chenopodium.—Oil of chenopodium won a place for itself in roundworm therapy on the basis of efficacy but did not hold it long after hexylresorcinol was made available in a satisfactory form for administration (see Hookworm for methods of using oil of chenopodium); *i.e.*, hexylresorcinol is preferred in private practice but in mass administrations in field work the drug is much too expensive and there oil of chenopodium has still to be preferred. Smillie (1942), while admitting the potentially greater toxicity of oil of chenopodium, nevertheless stated it to be the superior anthelmintic since one administration of it removes 90 to 95 per cent of the worms instead of the 80 per cent removed by a single administration of hexylresorcinol.

Santonin.—This is the oldest of the remedies for roundworm infestation and it is still much used because, being insoluble outside the intestinal tract and practically tasteless, it may be easily administered to children by incorporating the dose with a little sugar. Calomel, given to lessen absorption and to sweep out the stunned worms, may conveniently be added to this mixture; the commercial tablets containing $\frac{1}{2}$ grain (0.03 Gm.) of the drug and an equal quantity of calomel are so pleasing to children that they will eat too many of them if the supply is not carefully guarded.

Ransom, in his excellent treatise on the intestinal parasites of man, wrote of the use of santonin as follows: "It may be given in a dose of 1 to 3 grains (0.065 to 0.2 Gm.) to adults, mixed with an equal quantity of calomel, or to children at the rate of $\frac{1}{6}$ grain (0.01 Gm.) per year of age, also with calomel. This dose is given two or three days in succession and the treatment repeated in about ten days if eggs are still present in the feces." It is generally felt that castor oil may be substituted for the calomel in a dose of from 1 drachm to 1 ounce (4–32 cc.), depending upon the age and size of the patient, though there are some observers who doubt the safety of using the oil. If neither calomel nor castor oil has been used it is well to give a dose of magnesium sulfate several hours after giving the santonin. Preparatory semi-starvation is not so necessary with this drug as with some others; it may be given several hours after breakfast with calomel or late at night after a light supper with calomel and with a magnesium sulfate purge also in the morning.

Very large doses of santonin have often been given without untoward results, while small doses have not infrequently caused severe poisoning. It is a tricky drug and it is doubtful if one can with impunity exceed 3 grains as the maximum adult dose. I have so often recounted to my students an astonishing and illustrative experience which befell me during a brief sojourn as ship's surgeon in the tropics, that I would feel quite remiss if I failed to place it on record here. One day, off the coast of Ecuador, a Mexican fireman appeared at my door and announced that he had "borned a bug." Being entirely without understanding of his meaning, and furthermore altogether fearful of the volubility which I knew would greet an attempt to question him in my sorry distortions of his native language, I merely signified a desire to be led to the scene of this delivery. Whereupon he promptly conducted me to the after part of the main deck, where, surrounded by a gleeful group of his fellow-countrymen, a large roundworm lay in the scuppers. And before I could quite realize the significance of the scene, he began obligingly to cough and retch—and in a moment, with the assistance of two fingers inserted into his throat, he had brought up another! But now for the illustrative part of the tale, so far as it concerns the drug under discussion. This man gave a history of malaria which had been "cured" two years before, and was certainly not suffering from any

sort of febrile disturbance at the time of this incident; furthermore, at the examination of the crew six weeks previously, and often in deck encounters since, I had remarked him as an exceptionally robust and hearty fellow. I therefore gave him 5 grains of santonin, 3 grains of calomel and a little sugar—with the result that within the hour he was in convulsions, from which he went into coma, and only escaped foregathering with his Aztec fathers because they seemed not quite ready to call him in. Moral to adorn a dull tale: never give 5 grains of santonin to any man alive *if* it is desired that he continue in that condition.

THE PIN-, THREAD- OR SEATWORM

Enterobius (*Oxyuris*) *vermicularis* is a frequent infester of the anal region in infants and young children all over the world, but perhaps most frequently in the warmer climates. Adults do not harbor this worm so often as children do, and among the latter it is more commonly encountered in the city than in the country. An intermediate host is unnecessary, the entire life cycle being passed within the infested individual. The vicious circle is as follows: when the eggs are swallowed, the worms hatch and develop in the small intestine and appendix, but when mature they pass down to the lower part of the large intestine; when the females are ready to deposit their eggs they crawl out of the anus and wander about the perineum, even entering at times the vagina; the crawling of the worms in the rectum and on the perineum causes intense itching; in the process of scratching many of the females are crushed and their eggs liberated; the hands, contaminated with eggs, are ultimately carried to the mouth, and the whole circle is completed with the reinfestation which thus takes place. Recent studies have also shown that viable eggs contaminate the lower objects in rooms also, such as furniture legs, rugs, window ledges, etc.; Cram (1943) even found the eggs at all levels from floor to ceiling. Severe anal pruritus is the only definite symptom of pinworms, though it is perhaps not entirely incorrect to ascribe some of the nervous disturbances of young children, especially those with erotic manifestations, to this infestation. Jacobs (1942) felt, as the result of a study of a large number of infested children, that the following should lead one to suspect pinworm infestation: vaginal discharge, attacks of abdominal pain, anorexia, undernutrition, insomnia, nervousness, enuresis and pruritus ani; Cram (1943) agreed in the main except for the matter of the incidence of enuresis. Some observers believe that the worm is responsible, directly or indirectly, for many cases of appendicitis, but this is certainly not proved though the worms are many times found in that appendage when it is removed. Diagnosis is made upon finding the eggs in the feces by the salt flotation method, but the more frequently employed methods nowadays consist in applying an NIH swab to the perianal region (a glass rod to which is attached a small square of cellophane; this is stroked outward over the perianal mucosa and the cellophane square is then transferred to a glass slide and examined under the microscope), or the use of scotch cellulose tape applied to a wooden applicator in much the same way. A single NIH examination is from 40 to 50 per cent efficient; many observers have confirmed the finding of Sawitz *et al.* (1939) that seven such swabbings, on alternate mornings, will detect practically 100 per cent of infestations.

THERAPY

The length of the life cycle of the pinworm, from the time the eggs are ingested to the time the females crawl out the anal opening, was formerly held to be a little more than two weeks. If, therefore, the conveyance of eggs from anus to mouth by contaminated fingers could be *absolutely* prevented for a period of two to three weeks, it was thought the infestation would be cured. Now, however, with some investigators maintaining that the cycle may be several months in length and others that in some instances the eggs may be laid within the bowel and the cycle be completed there, the hope of curing the patient with hygienic measures rigidly maintained during the period covered by one complete cycle is waning. However, I shall continue to describe the methods, even though the feat is extremely difficult of accomplishment, none the less so because viable eggs are now known to survive quite a while on carpets, furniture, etc.

The treatment should begin with a full bath with soap and water, special attention being paid to the anal region. After this the anal region and the perineum are to be anointed with an ointment composed of 2 per cent of ammoniated mercury in equal parts of lanolin and petrolatum, a pad of cotton applied, and the child clothed in heavy drawers that are closed front and back. After each defecation the anal region is to be thoroughly washed with soap and water, the ointment and a fresh pad applied, and the drawers put on again. At night, when the itching is at its worst, the following anesthetic preparation may be substituted for the mercury ointment.

℞	Ethyl aminobenzoate (benzocaine)	gr. xlv	3.0
	Salicylic acid	gr. xij	0.78
	Hydrous wool fat (lanolin)	℥ss	15.0
	Petrolatum to make	℥j	30.0

It may be necessary to tie the hands, especially at night, so that they cannot be carried to the site of itching. In any case, the cleansing of the hands is of the utmost importance since ordinary washing will not suffice to rid them of the eggs. They must be *thoroughly and frequently* scrubbed with brush, soap and water, and the nails kept scrupulously clean. Daily full baths are desirable. All of the members of the family and any closely associated individuals must be simultaneously treated else mutual reinfestation will be certain to take place. Bed sheets should be boiled at least twice weekly.

It is believed that a low carbohydrate diet is of advantage in these cases, but I know of no careful studies showing that this is true.

Internal Medication.—It is the usual practice to use vermifuges by mouth in the treatment of pinworm but their record in the past has not been brilliant. Considerable success, however, has been obtained in recent years with *gentian violet*. Wright and Brady (1940) treated 224 patients with this drug, giving adults 2 enteric-coated tablets of ½ grain (0.03 Gm.) three times daily before meals, and children ⅙ grain (0.01 Gm.) a day for each year of apparent (not chronological) age, the total daily amount of the drug for children being also divided into three daily doses. Their best results were obtained when the treatment was continued for ten consecutive days. Nausea, vomiting, abdominal pain, diarrhea, headache and dizziness sometimes accompanied this medication but subsided quickly when dosage was reduced or the drug was omitted for a day or two. Brady (1941) said that the contraindications to gentian violet therapy are concomitant infections with *Ascaris lumbricoides*, gastro-

intestinal, cardiac, hepatic, or renal disease, and pregnancy. Alcohol should not be used during the period of treatment. Cram (1943), summarizing nearly two decades of the studies on enterobius in the National Institute of Health, stated that the results obtained with gentian violet are superior to those with any of the other methods of therapy; Wright and Brady's proportion of cures was 84 per cent. All of the other anthelmintic drugs—santonin, oil of chenopodium, tetrachlorethylene, and so on—have been tried but none has made such a good record as this. Phenothiazine has interesting possibilities as an anthelmintic, but the studies of both Most (1943) and Bercovitz *et al.* (1943) certainly indicated that the agent is sufficiently toxic to warrant the limitation of its employment as yet to special clinical investigations.

Rectal Medication.—The female oxyuris is difficult to discourage in her egg-laying orgies about the anus. Many formulae have been employed, of which I can list but a few here; they are all intended for use every day or every second day over a long period of time. The quantity administered should be sufficiently large that retention cannot occur, though the patient should be instructed to resist expulsion as long as possible.

Saline.—Six per cent aqueous solution of sodium chloride (approximately 15 teaspoonfuls of salt to the quart of warm water).

Quassia.—Two ounces (64 Gm.) of the chips are to be added to 1½ pints (750 cc.) of water and boiled down to 1 pint (500 cc.), stained, and introduced when cooled to body temperature. This infusion may be made in saline, as above, instead of water.

Salicylic Acid.—The following formula is used:

Salicylic acid	ʒss	2.0
Sodium borate	ʒss	2.0
Water to make	Oj	500.0

Introduce warm, using half quantities for young children.

Soap.—The ordinary warm soapsuds enema is employed; many of the females are believed to be killed by 1 per cent soap solution.

Vinegar.—Ordinary table vinegar in the proportions of 30 to 100 parts to 1000 parts of warm water.

Quinine.—Any of the quinine salts may be employed in 1:2500 to 1:1000 aqueous solution. The possibility, which is not at all remote, of inducing cinchonism must always be taken into account.

Hexylresorcinol.—Following a soapsuds enema, a 1:2000 solution of crystalline hexylresorcinol in water is given as a high enema to be retained as long as possible; the treatment is repeated every other night for several weeks.

WHIPWORM

Trichocephalus (*Trichuris*) *trichiura* is a very common worm all over the world, but is most frequently harbored in warm climates. Smillie stated that it is probably the most widely distributed worm in the United States except the roundworm; Moss (1939), in a routine stool examination of 2265 dispensary patients in New Orleans, found it more prevalent than roundworm. No intermediate host is required to complete the life cycle of this worm. Infesta-

tion takes place when the eggs, which are distributed in human feces, are swallowed in contaminated water or upon uncooked food. The adult worms inhabit the cecum and appendix principally. *Trichocephalus* only very rarely causes symptoms and when they arise they are very variable; in Swartzwelder's (1939) analysis of his 81 uncomplicated cases the most frequent symptoms were abdominal, with also headache, backache, anorexia and loss of weight. For the most part, however, the worm seems to be harmless—if, as is extremely improbable, one is justified in considering harmless any parasitic invader of the body.

THERAPY

In answer to a query in the Journal of the American Medical Association in mid-1944, the following measures were recommended as those most likely to accomplish elimination of whipworm: (*a*) Place the patient on a light diet for two days and then the night before specific medication purge with magnesium or sodium sulfate, and, following good elimination, give a high enema of isotonic physiologic saline solution to clean out the residue of viscous feces which remain attached to the worms. (*b*) The following morning the patient should remain in bed without breakfast and should be given 10 minims (0.6 cc.) of tetrachlorethylene and 2 minims (0.12 cc.) of oil of chenopodium, which should have been thoroughly mixed and added to sugar in a teaspoon. (*c*) Two hours after administration of the anthelmintic there should be given a follow-up saline purge, and then following the bowel movement a light noon meal may be taken.

Caldwell and Caldwell (1929) found that the fresh sap of a fig tree, *Ficus laurifolia*, peculiar to certain river valleys of Colombia where it is known as "Leche de Higueron," would remove 85 per cent of the whipworms in a single treatment. Robbins (1930) isolated the active principle, ficin, from this agent but it proved to be a proteolytic enzyme which will attack and digest the stomach and intestinal mucosa if small lesions are present. The studies of Molitor *et al.* (1941), employing laboratory animals, did not indicate that the employment of ficin in its present form is likely to become a practicable measure.

GUINEA OR MEDINA WORM

Dracunculus medinensis is a large worm that requires two hosts for the completion of its life cycle. The free-swimming larvae penetrate and develop to a certain stage within the body of a very small crustacean of the genus *Cyclops*. When unboiled water containing this crustacean is swallowed man becomes infested. About a year after the ingestion of the larvae, the adult female worm works her way into the subcutaneous tissues in order to discharge her embryos outside the human body. Her presence is first manifested by the pruritus which is set up, then a cordlike lump can be felt beneath the skin; finally, there is a vesicle and then an ulcer, from an opening in the base of which the embryos are liberated in a milky fluid which exudes when cold water is brought into contact with the ulcerated surface. The infestation of the primary crustacean host is easily accomplished by reason of the fact that most of the ulcers—there may be several in one individual—are upon the feet and

ankles and are discharging continuously whenever the patient is wading through fresh water. There is a very pronounced eosinophilia but constitutional symptoms are slight.

Guinea worm is harbored in Arabia, Iran, Turkestan and India; it is present in various parts of Africa, being particularly prevalent in the Nile Valley; in South America, it is endemic in the Guianas and in certain districts in Brazil; it seems to be disappearing from the West Indies, which were formerly heavily infested; a few cases have been reported in the Netherlands Indies. It is of interest to note that Chitwood (1933) found a worm morphologically identical with *D. medinensis* in the fox, raccoon and mink in several parts of the United States and Canada, and that Chandler (1942) confirmed the finding in raccoons; all the human cases reported on this continent have been imported, however.

THERAPY

The natives everywhere effect the extraction of the worm by slowly winding it out around a small piece of wood. The process requires about two weeks and is open to the serious objection that if the worm breaks, as very frequently happens, secondary infection and a stubborn type of suppuration are almost certain to take place. Manson-Bahr (1940) said that on the Gold Coast the natives rub the site of a presenting worm with olive oil, and subsequently mercurial ointment, daily and vigorously for a week or more; this is said to kill the underlying worm, which is then extracted. The orthodox physician's most usual method of attack is to inject 1:1000 solution of bichloride of mercury into the burrow, the attempt, which is usually unsuccessful, being made to remove the worm on the following day. One of my former students informed me several years ago that in Hong Kong the worms are caused to extrude in their entirety by keeping the ulcers covered with plain cold water dressings continuously for ten days to two weeks. Ransom states that Macfie had good results with the intravenous injection of tartar emetic, 1 grain being given every second day until a total of 6 grains had been given, but I do not know that anyone else has had this experience. Elliott (1942) described the successful employment of phenothiazine in an elaborate injection technic, but until it is proven that the toxicity of this agent is sufficiently low to justify its employment it does not seem to me that the method needs to be described here.

TRICHINOSIS

Trichinosis is a disease that is acquired when the encysted larvae of *Trichinella spiralis* are ingested. The larvae are liberated by the action of the digestive juices, the adult worms quickly develop in the upper part of the intestinal tract, copulation takes place, the males die and the females burrow into the submucosal tissues whence they discharge the new crop of embryos into the lymph spaces. These embryonal forms are carried into the blood stream, which conveys them to all parts of the body; some of the embryos also undoubtedly penetrate through the tissues by their own motile power. Ultimately they come to rest in the voluntary muscles, principally of the lower extremities, where the developing larvae give rise to an inflammatory reaction and are finally

walled off by connective tissue, sometimes with calcification in addition. An individual cyst is barely perceptible to the naked eye. This process goes on in the rat, the pig and in man. The pig acquires the cyst through eating the carcass of an infested rat or other meat-eating mammal, or through eating trichinous pork in raw garbage or in the offal at time of slaughter, while man acquires it by eating the uncooked or insufficiently cooked flesh of the pig or occasionally of another animal such as the bear; but just how the rat acquires it is not so clearly known. Certainly his opportunities are sufficiently great, however, for the larvae have been found in the flesh of twenty-five different mammals; this rodent is also not above eating the flesh of its own kind. That the parasite is transmitted only by the ingestion of infested flesh is practically certain, for all attempts to perpetuate the disease by fecal contamination have failed.

The symptoms in man are caused by the presence of the worms in the intestinal tract, by the presence of larvae in the muscles and elsewhere, and through the action of toxins which are liberated by the worms themselves, and by the extensive destruction of muscle tissue. From three days to three weeks (twenty-two days or less in 98 per cent of the 156 cases studied by McCoy, 1942) after the ingestion of trichinous pork the patient is seized with nausea, vomiting, intestinal cramps, and usually either diarrhea or constipation and tympanites. There are also chilliness and sweating and a fever which much resembles that seen in typhoid; many times a typhoid-like skin eruption also appears. Edema around the eyes, but often involving the whole face and the lower extremities as well, is a characteristic feature of the disease, as is also tenderness of the muscles near their tendinous attachments. Diplopia is sometimes complained of early in the attack. There is usually a pronounced eosinophilia, beginning in the second week. The encysted larvae may be found in an unstained teased or sectioned bit of muscle tissue that has been removed under local anesthesia; sometimes active embryos are demonstrable in the blood and spinal fluid. In the most exhaustive study of the diagnostic intramuscular skin test that has been published to date—that of Gould (1943), who studied routine autopsy material from 1231 persons, did skin tests on 3010 persons who did not come to autopsy, and compared autopsy material and skin tests in 388 patients who had been skin tested before death—the claims made by earlier workers for reliability could not be confirmed. Suessenguth and Kline (1944) have evolved a flocculation slide test which in their hands possessed a high degree of specificity and sensitivity. Symptoms of encephalomyelitis, anterior poliomyelitis, polyneuritis, optic neuritis, cranial nerve paralysis, meningitis, and symptomatic psychosis without any focal signs have all been recorded, and bronchial and pulmonary signs are present in about 50 per cent of cases. Myocarditis is one of the most serious complications; Spink (1935) felt that the histologic picture in the myocardium was not positive, but Terry and Work (1940) seemed to be in disagreement. Gould (1943) said that most deaths are due to lesions of the heart or the lungs.

The mortality in trichinosis is usually stated to be about 5 per cent, but bearing in mind that the disease is always mild in children and that many adults undoubtedly have undiagnosed slight attacks, it is very probable that we can really have no true notion of the total mortality in the disease. On the other hand, in family or neighborhood outbreaks in which large quantities of a particularly bad lot of meat have been eaten raw or nearly so, the death rate has frequently been from 50 to 100 per cent. The duration of the disease

in nonfatal cases in such outbreaks is very variable; an individual may completely recover in a few days, or he may lie in a state much resembling that of typhoid fever for several months; however, Gould (1943) found that most deaths occur from the fourth to the sixth week. Post-trichinal "rheumatism" is often alleged to persist for many years after recovery from the acute attack, but none of Bercovitz's (1940) carefully studied 70 patients had residual symptoms of any sort lasting more than a year. Reimann *et al.* (1943) felt that there is a possibility that trichinosis as a disease with strong allergic manifestations may in certain instances serve as one cause of the syndrome called periarteritis nodosa.

In 1937, Magath asserted that from 10 to 20 per cent of the adult population of the United States have acquired trichinae, most individuals, however, having had no intimation of the infestation; he well made the point that there is still need of emphasizing to all classes the importance of cooking pork thoroughly before consuming it. The review of Lewis *et al.* (1940), and the much more extensive one of Wright *et al.* (1943), indicated that Magath's figures were not too high. Van Someren's (1937) study of 200 diaphragms in England, where the law compels the boiling of all garbage before its use in feeding hogs, revealed an incidence there of only about 1 per cent; just how this author would justify his statement that "the general level of hygiene and habits of the British people probably plays the principal part in reducing risk of infection" I am sure I do not know. The incidence used to be very high in parts of Germany, but what it is today of course we do not know, nor are there accurate figures available for most of the rest of the world.

THERAPY

The specific treatment of trichinosis is in a most unsatisfactory state, or perhaps one should say a negative state, for the truth is that all measures have completely failed. All the vermifuges have had their advocates, but none has been shown to have any consistent value, bearing in mind that results in single cases are not significant in a disease whose severity and mortality are as variable as they are here. Roentgen ray and radium have failed, as have also the arsenicals, tartar emetic, the dyes and the sulfonamides. A satisfactory antiserum has not been produced; convalescent serum has not had sufficient clinical trial to enable us to adjudge its value.

In the beginning, *i.e.*, while gastro-intestinal symptoms are prominent, all writers are agreed that the patient should be thoroughly purged. Three grains (0.2 Gm.) of calomel, or 1 ounce (32 cc.) of castor oil, should be given, to be followed in either case in four hours by $\frac{1}{2}$ to 1 ounce (16–32 Gm.) of magnesium sulfate or an equivalent dose of some other saline. The parasites may live for five to seven weeks in the intestine, and it is at least possible that such females as have escaped impregnation, and have therefore not burrowed into the submucosa at the time of diagnosis, may be swept out of the tract by this purgation. If the case is a severe one, the best symptomatic treatment is believed to be that employed in the handling of a case of typhoid fever, without of course the stringent aseptic and antiseptic precautions which are necessary to prevent the spread of this latter disease.

FILARIASIS AND ONCHOCERCIASIS

Filaria (*Wuchereria*) *bancrofti* is a small worm that lives in the lymphatic glands and vessels of man. The female worms give birth to living microfilariae that pass their life in the blood stream; during the day they accumulate in the lungs, the heart and the large thoracic vessels, but at night they come out into the general circulation in large numbers. If the infested individual reverses his diurnal scheme, the embryos accommodate themselves to the reversal and appear in the blood stream during that portion of the twenty-four hours in which the patient is sleeping. The cause of this periodicity is not known and it is a noteworthy fact that it does not characterize infection acquired in the South Central Pacific islands. When infested persons are bitten by any one of a number of genera of mosquitoes, but principally one or another of several species of *Aedes* or *Culex* (Byrd *et al.*, 1945, found *Aëdes scutellaris var. pseudoscutellaris* to be the only transmitter of importance within the Samoan area), the larvae enter the body of the mosquito and undergo certain changes there; the metamorphosed larva, being deposited upon the skin of another individual, which the mosquito bites at a later period, pierces the skin and enters the lymphatics, there to grow to adulthood and send showers of microfilariae into the blood stream. It is felt that the acute symptoms of the disease, which rarely occur before an individual has been about three months' resident in a filaria infested region, are the result of irritative changes set up by the live adult filariae in lymphatic tissues and by allergic reactions to the dead adult filariae in the same location; plugging of the lymphatic channels causes a backing up of toxic products centrifugally, which would account for the so-called retrograde lymphangitis. Zuckerman and Hibbard (1945), in confirmation of Wartman (1944), found no histologic evidence of superimposed bacterial infection as a cause of lymphangitis in their series of cases. The microfilariae do not cause symptoms unless they may in some instances be responsible, as Neumann (1944) considered possible, for the giddiness which is a frequent complaint in endemic areas and rarely for the occurrence of retinal hemorrhages without other explanation. An acute attack ("mumu") consists of lymphangitis of an arm or leg, or more often of the scrotal region or the scrotal contents, accompanied by constitutional symptoms which in most instances are not very severe. The affected part is of course enlarged and erythematous and the lymphatics and regional glands are swollen and tender. The symptoms disappear completely in a few days, sometimes with subsequent intense itching and desquamation, but the patient is likely to experience many of these attacks and if he remains in an infested region it is finally noticed in a large proportion of the cases that the swelling is not entirely subsiding in the intervals. Ultimately in a native or in a foreign long-time resident of an infested area attacks cease to recur but the chronic deforming enlargement, known as elephantiasis, remains. The establishment of elephantiasis seems to bring about the death of the adult worms and thus to cause the disappearance of microfilariae from the bloodstream. Next in frequency to the legs, the scrotum is involved; elephantiasis of the arms, the penis, the scalp, the breasts and the subcutaneous tissues have also been reported. Chyluria is usually a symptom of the disease in these advanced cases, due to the blocking of the thoracic duct and the bursting of some of the bladder lymphatics. Large boggy swellings in the groin are frequent, and filarial hydrocele and orchitis are not uncommon. Leg abscesses in filariasis patients often contain portions of dead worms.

During our campaign in the South Central Pacific during War II many thousands of our Army and Navy personnel contracted filariasis and the following pertinent facts were discovered or stressed during the investigations which took place as a result of these infestations: (*a*) The search for microfilariae in the blood of temporary residents in an endemic area yields only negative findings for the reason that, according to Neumann (1944), these forms are usually not found before the seventh year after infection has occurred. Dickson *et al.* (1943), studying this matter in a highly endemic area, found microfilariae in only 1.6 per cent of 244 children under five years of age. A negative finding does not of course mean that the individual does not have the disease but only that sufficient time has not yet elapsed for the number of microfilariae to have risen sufficiently high for their easy detection to occur; it is highly probable that the female adult worm, which may be seen under the microscope to give birth to great swarms of microfilariae, does not behave so *in vivo*. It is further possible, as pointed out by earlier observers, that marked tissue reaction around the adult worm hinders access of the microfilariae to the circulation. (*b*) The diagnosis of an early case rests principally on the clinical findings because neither the complement fixation test nor the several intradermal tests have as yet proved very satisfactory. (*c*) A non-native resident of an endemic area is well advised to leave the region if possible after he has had an attack because the likelihood of ultimate elephantoid deformity increases with an increasing number of attacks. (*d*) The disease continues active for some time after return from an endemic area, though Huntington *et al.* (1944) thought that activity was subsiding in most of the Navy personnel under their care in the continental United States after four months away from the islands and Johnson (1944) found that improvement in such groups occurred in direct ratio to the period of time spent within the United States. However, Huntington *et al.* cited one patient who was under their care at the time of writing who continued to show marked activity ten months after leaving the area. (*e*) Once the attacks cease in an individual who has left the endemic area it appears that further increase of elephantoid swelling if any had occurred need not be expected; indeed, Neumann (1944) said that the existing elephantoid state may even lose its turgidity and the tissues become gradually flabby and the skin loose. (*f*) The likelihood of the development of serious elephantoid deformities in any of our military personnel who have been subjected to heavy filarial infections for only a limited period of time is considered to be very small, but Rome and Fogel (1943) and McIntire (1944), among others, have indicated the nature of the major psychoneurotic problem posed by men who have been so infected and who have seen the dire results of continuous reinfection over the years in native populations. (*g*) Sawyer (1944) stated the authoritative opinion that the return to the United States of large numbers of individuals infected with filariasis will not cause a serious new disease problem here even though some of our nuisance mosquitoes are capable of transmitting this infection. The reasons for this are several: in the first place, practically none of our returning troops have microfilariae in their blood; the peculiarities of the mosquito transmission of this organism make it extremely unlikely that such transmission could be sustained in this country for very long even though there were to appear a number of microfilariae carriers among us; large numbers of residents of infected Caribbean islands have come to the United States and made their homes here in recent years but have not given rise to fresh cases of filariasis in this country, though many

of these individuals had come here because they had experienced early infection in their own native region; a focus of infection existed for a good many years in Charleston, South Carolina, but it never rose above a smouldering stage and has now died out; a few infections presumably acquired in regions in the United States other than Charleston, South Carolina, have been reported but the number is much less than a dozen and they do not fit into any present epidemiologic picture. (*h*) The studies reviewed by Hawking (1943) proved that microfilariae introduced by blood transfusion can live in the blood of a nonimmune subject for as long as eight days; however, the disease filariasis cannot be so transmitted since its etiologic agent is the larval form of the filaria after it has undergone certain changes in the body of its insect vector.

Filaria loa spends its larval stage in the blood, with the diurnal periodicity of *F. bancrofti*, but wanders about in the subcutaneous tissues during its adult life. The name "Calabar swelling" has been applied to the fleeting edemas which it causes during the course of these wanderings; areas of localization in the spleen may also react with inflammation and fibrosis. The parasite sometimes crosses the eye, giving rise to conjunctivitis during its passage. A fly of the genus *Chrysops* is the vector of this form of filariasis.

Filariasis due to *F. bancrofti* occurs in the tropical belt all around the world, but the distribution of endemic centers within this belt is a very unequal one; it is not possible to mention, in a work so limited as the present one, all the places where this disease has been diagnosed. Statistics as to incidence and mortality are of doubtful value since many individuals seem to be able to harbor the adult worms and the microfilariae without ever manifesting any symptoms. Filariasis caused by *F. loa* is confined to a very small area on the West Central Coast of Africa, cases occasionally turning up in our country in returned missionaries; I saw one such case here in Milwaukee some years ago.

In Guatemala, and in certain southern provinces of Mexico, Strong (1931–1938) and his associates investigated a disease characterized by the presence of subcutaneous fibromatous nodules on the head, and in many cases disturbances of the eyes and loss of vision. They found that the tumors contain adult male and female *Onchocerca caecutiens*, and that not mosquitoes but three species of *Simulium* flies are concerned in the transmission of the disease. Dampf (1942) felt that *Onchocerciasis* will certainly spread along the Pan-American Highway unless certain definite precautions are taken. In some portions of tropical Africa essentially the same disease prevails, but the filarial parasite there is *O. volvulus* (which Van den Berghe, 1941, who has studied the matter intensively, considered indistinguishable from *O. caecutiens*), and the nodules occur on the body more often than on the head. Apparently in Africa there is also a reservoir of the disease in cattle and certain of the larger wild animals, notably antelopes.

THERAPY

The symptomatic treatment of early filariasis involves no especial difficulty as the attacks are of short duration though often very distressing in nature. O'Connor and Hulse (1935) confirmed in Puerto Rico what others had observed elsewhere, that the taking of a purge when the attack threatens mitigates the symptoms and lessens their duration—though it is certainly difficult to understand how or why this should be so. Rest in bed is usually self-imposed, but resort to analgesic and sedative drugs must many times be made. The involved part is relieved by elevation and cold applications. In the lymphan-

gitis of the cord that often accompanies filarial orchitis the pain is sometimes so great that large doses of morphine are required to give relief. It has been said that chyluria may at times be controlled by elevation of the pelvis and reduction of the fat in the diet, but Mohadevan (1941), in a symposium on filariasis in India, expressed the opinion that fat should not be excluded from the diet of a chyluric patient for the reason that he is already losing much of what he should have retained.

Employment of the sulfonamides or arsenicals during the early attacks has not usually been rewarded with success; indeed, during War II out in the Pacific attacks of acute lymphangitis were reported as occurring in individuals while under treatment with the sulfonamides or mapharsen. A hopeful contribution was made by Brown (1944), who used anthiomaline (lithium antimony thiomalate) on 12 filariasis patients in the Virgin Islands who had microfilariae in their blood. The adult dosage employed was 3 cc. which was injected intramuscularly at daily intervals, using only a half-size dose to ascertain sensitivity at the time of the first injection, until quantities ranging from 15 to 48.5 cc. (averaging 38 cc.) had been given. The microfilariae counts in these patients were reduced 85 to 100 per cent and the reductions had been maintained from four to five months at the time of Brown's report, this being taken to mean that a corresponding number of the adult worms had been killed. One patient however failed to respond at all to the treatment. With the exception of one patient who had greatly enlarged inguinal and femoral lymph glands, and another with enlarged glands and scrotum, the only evidences of filarial infection in this series of patients were the microfilariae in the blood and a slight but definite general glandular enlargement with a history of recurrent lymphangitis. No reduction in the size of the enlarged lymph glands or of the enlarged scrotum in the one patient could be detected following treatment, though it was said that one patient noted a pronounced improvement in his inguinal distress on exercise. Forty per cent of the patients experienced vomiting and epigastric pain as a result of the employment of the drug; a minority of them experienced a gluteal reaction which caused them some inconvenience; two patients had fever; one patient developed arthritic symptoms; one patient experienced a diminution in kidney function; 6 of the 12 patients had transitory itching rashes after a number of the injections—Brown did not consider these toxic manifestations sufficient to preclude the continued trial of anthiomaline in filariasis. This work of Brown's is of great interest but I think that Coggeshall (1945) did well in pointing out that it is of limited importance unless it can be demonstrated that anthiomaline destroys the adult worm, since the microfilariae do not themselves give rise to symptoms.

In 1934, Golden and O'Connor were somewhat encouraged by the results of roentgen therapy applied locally over fairly large areas. It seemed that at the time Japanese observers were also using this method of treatment, but I have seen no subsequent reports other than the statement of Burhans *et al.* (1944) that they had tried x-ray therapy in Navy personnel and found it to cause prompt decrease in the size of enlarged lymph glands. It is to be hoped that the results of a really definitive study of this type of therapy will be published in the near future.

The treatment of elephantiasis is principally surgical; scrotal cases give the most satisfactory results, but the operative procedures so far evolved apparently still leave much to be desired. Bowesman (1938) reported that the condi-

tion is simply and safely alleviated to some extent by weekly injections into the femoral artery of 2 to 3 cc. of sterile 10 per cent glycerin. Knott (1938) said that prolonged firm bandaging induces prompt symptomatic relief and effects gradual removal of the lymphedema.

In filaria loa disease the parasite may be removed by simple incision when it crosses the eye; its removal from the subcutaneous tissue is sometimes accomplished in the same manner.

In onchocerciasis, the tumors (and the contained adult parasites) can be easily removed under a local anesthetic, but in some cases the microfilariae continue to circulate in the body for at least several years. Chemotherapeutic agents have failed in this disease.

STRONGYLOIDES INFECTION

Physicians in the southern United States are becoming very familiar with this entity which has long been recognized in other subtropical as well as tropical regions. The life cycle of the causative worm, *Strongyloides stercoralis*, is much like that of its close relative, the hookworm, except that it embeds in the mucosa instead of lying free out in the lumen of the intestine, and that during the time in which the larvae are migrating from the capillaries into the bronchioles an acute inflammatory reaction may take place in the lungs; furthermore autoinfection can occur since the larvae are capable of penetrating the intestinal mucosa and the perianal skin to continue the cycle without going through a period of further development on the ground. In very light infestations there may be no symptoms, but in moderately heavily infested patients there is diarrhea with distress after meals, alternating at times with constipation; in severe cases there is intractable diarrhea, great emaciation and, occasionally, profound toxic edema. Positive diagnosis can be made only on finding the typical motile larvae in the stools, since the eggs closely resemble those of the hookworm. Whitehill and Miller (1944) reported a case and cited another from the literature in which the larvae of *S. stercoralis* were present in the urine.

THERAPY

The anthelmintic drugs have failed here since the worms are embedded in the mucosa and cannot be reached by an agent which is not absorbed.

Faust (1932) reported the treatment of about 200 cases in New Orleans with gentian violet, a method first reported by De Langen, in Java. Two ½ grain (0.03 Gm.) enteric-coated tablets of the medicinal dye are given by mouth to adults three times daily before meals for from seven to ten days (in 1939, Faust recommended that the course be continued for sixteen days). In a follow-up examination of 47 patients, all but 2 had been freed of the infection; in 4 cases, two courses of treatment were needed. Two patients reported mild nausea, but no other deleterious symptoms were observed. This treatment is said to kill the adult worms but not the larvae or the eggs. Kouri and Sellek (1936) also reported favorably. Hinman (1938) felt that possibly the drug was of some value in the 46 cases in which he used it; Levin (1938) said that 3 or more courses of treatment with gentian violet are necessary in order to obtain a negative stool, but he seemed to have accomplished this in only

10 of his 17 cases; Shikhobalova and Semenova (1942) found larvae reappearing one to two months after a course of treatment had ceased in some of their small series of cases. Faust (1939) said that in refractory patients 25 cc. of a 1 per cent solution of medicinal gentian violet can be introduced by transduodenal intubation, leaving the tube in for an hour after the introduction of the drug and then carefully withdrawing it. Simpson (1939) reported that he sometimes succeeded with the use of iodine: a saline is given in the evening, and the next morning, withholding breakfast, a duodenal tube is passed and the stomach is irrigated and the duodenal contents aspirated; then 4 cc. of compound solution of iodine (Lugol's solution) are introduced and the tube removed, the treatment being repeated on alternate days until the duodenal contents and stool are negative for ova, parasites and larvae.

HOOKWORM DISEASE

(*Uncinariasis, Ancylostomiasis*)

Hookworm disease is caused by two species of intestinal worms, *Ancylostoma duodenale* and *Necator americanus*. The life cycle of these worms is very simple, since man is the only host. The eggs are passed in the feces of an infested person; if the stool is deposited on the soil under suitable conditions of warmth, moisture and shade, larvae capable of infesting man develop in five days; this infestation takes place when soil, thus contaminated, comes into contact with the bare feet or with other naked portions of the body; the larvae then pierce the skin and enter the circulation, which carries them into the lungs, the alveolar walls of which are pierced in turn and the free air spaces entered; in the next stage the larvae pass up the trachea and larynx and then down through the esophagus and stomach into the middle portion of the small intestine, where they attach themselves and attain maturity. From six weeks to two months after the larvae have penetrated through the skin the adult female worms are laying eggs which are passed out with the feces. Individual worms live as long as seven to ten years, during which time they disengage and reengage at many sites in the intestinal mucosa. The worm passes much blood through its body and each time the head is withdrawn a point is left which bleeds for some time, as the head of the worm secretes an anticoagulant substance. It has been felt in the past that these worms secrete a hemolytic toxin, but as the point has never been proved the consensus is now that the anemia of hookworm infestation is due entirely to gross loss of blood as described above. Bonne (1942) alleged that occasionally in *A. duodenale* but not in *N. americanus* infection the worm may invade the submucosa of the intestine and give rise to inflammatory reactions there.

Hookworm disease prevails throughout the tropics and also in many warm, but distinctly subtropical, regions. It is principally a disease of "native" populations, but Manson-Bahr (1940) warned that it may occur among "Europeans" in infested regions even though their personal habits would seem to exclude the possibility, the infestation occurring in these instances, in his opinion, *via* the mouth. Endemic foci also exist in the Witwatersrand gold mines in the Transvaal and in the coal mines of such of the cooler portions

of the globe as central Europe and the south of England. Miners contract the disease by contact of their hands, arms, knees, elbows, or buttocks with feces-contaminated soil in the mines, but everywhere else it is almost exclusively contracted by those who go about barefooted in regions where the first principles of decency in the matter of personal and communal hygiene do not obtain. That is to say, in the tropics where poverty forces the native to go barefooted and custom permits him to defecate where he pleases, there, other things being equal, hookworm disease will prevail. But that very similar conditions obtain in more "enlightened" communities is certainly a blot upon civilization's record. Hookworm problems which vary in extent in different regions still exist over large areas in our South, but the analysis of Keller *et al.* (1940) indicated that in six of the most badly infested states there had been an average decrease of 68.3 per cent in incidence since the campaign for the control of hookworm disease by the Rockefeller Sanitary Commission (1910–1914).

Infestation of individuals begins as soon as they are old enough to range very far away from the house door and continues as long as they go about barefooted in the endemic region. The passage of the larvae through the skin causes in most cases a local vesicopustular lesion known as "ground-itch." After a variable period of time, depending upon the degree of the infestation and the individual's resistance, the symptoms begin gradually to appear. At first there are slight gastric disturbances, which disappear upon the taking of food; then the individual develops a desire for unusual articles of diet, such as clay, chalk and hair. This symptom is often denied by patients, but in some regions the craving is openly confessed and pandered to, as in mid-Java, where, according to Darling, a certain lumpy earth of volcanic origin is kept on sale in the shops. Pallor appears, there is dizziness and palpitation and breathlessness on exertion, oftentimes the pulse is erratic and sometimes there is a low-grade intermittent fever, and the patient becomes mentally dull and indifferent and physically less and less suited for the more arduous forms of labor. Examination of the blood reveals a reduction in the hemoglobin which is out of proportion to the reduction in the number of erythrocytes, and sometimes eosinophilia; the stools contain many hookworm eggs. If the patient is a child he is often pot-bellied and much below the average in size. Thus stunted mentally and physically, weak, anemic, shiftless and indifferent, the hookworm victim goes through life, an economic drag upon the region which, in his ignorance, he continues to pollute; but he seldom dies of his malady. In the tropics, however, where infestation is much heavier than in the temperate zones, death primarily due to hookworm disease is not rare; the terminal picture is said to be one of extreme anemia and physical exhaustion, a nephrotic syndrome with changes in renal function, anasarca and cardiac failure. Ashford *et al.* (1933) performed a very great service by placing on record 7 cases acutely and massively infected from the same source; during the first week there was much discomfort from dermatitis and at the end of this period soreness in the throat and a feeling of having caught cold. Within another week great weariness and fleeting epigastric pain had appeared, which was followed by colic, great loss of weight, strength and color, and in all save one case by diarrhea; loss of blood in the stool was alarming in several cases and all became seriously anemic.

It is thought the mysterious AAA disease of the Ebers papyrus, dating from the Egypt of about 1550 B. C., might have been hookworm; other intestinal

worms are with certainty mentioned and prescribed for in that ancient compilation. As century followed century, from being known as Egyptian disease it came to be called tropical chlorosis, miner's anemia and St. Gotthard tunnel disease. In 1843, Dubini described *A. duodenale*, and in 1866 Griesinger showed its causal relation to the disease. *N. americanus* was discovered by Stiles in 1902. In 1898 Looss discovered the remarkable route by which the larvae reach the intestine.

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Extensive experience in the campaigns for control of this malady has conclusively shown that routine drugging of individuals who must remain in endemic regions is of secondary importance to the sanitary measures necessary to prevent reinfestation. Still today, however, both within and without such regions, chemical disinfestation must often be resorted to. Wickramasuriya (1937), whose experience in Ceylon has apparently been vast, stated unequivocally that the fear of abortion or miscarriage resulting from the treatment of hookworm disease in pregnant women is groundless, and furthermore, since hookworm disease has a very deleterious influence on pregnancy, and vice versa, pregnancy should be regarded as a special indication for the use of the effective anthelmintic agents. The following are the chief of these agents. Their toxicology is presented at the end of this chapter.

Tetrachlorethylene.—The superiority of this drug seems to be well established upon the basis of its ease of administration, relatively low cost, low toxicity and relatively high efficacy in eradicating the worms in a single treatment. Smillie (1939), who has had wide field experience, spoke very highly of this drug. Andrews (1942) said that a single treatment would not get rid of the last hookworm from more than 50 per cent of his patients but that it would remove about 90 per cent of all hookworms, and that furthermore two treatments with tetrachlorethylene are about equivalent to and much safer than a single dose of carbon tetrachloride in dislodging hookworms. It is probably advisable to clean out the intestinal tract by a magnesium sulfate purgative the evening before (though this may be omitted), the treatment being given next morning, omitting breakfast. The average adult dose is 3 to 4 cc. divided into 6 capsules, or the liquid may be poured onto sugar. Immediately after taking the drug a magnesium sulfate purge is taken. Or the drug may be added to the saline and the two taken together, rinsing the glass with water and swallowing the rinsings also. The patient should rest after taking the dose and may eat after purgation has occurred. If ova are found in the stools upon reexamination after two weeks, the treatment may be repeated. The dosage for children is 0.2 cc. for each year of age up to fifteen. The drug has a more pronounced taste than carbon tetrachloride, but as pointed out by Hare and Dutta (1939) it is pleasant to smell, does not burn the mouth and produces a slight drunkenness enjoyed by coolie populations; Lambert (1933) had earlier referred to this intoxicating action but also not as an objectionable feature. Castor oil is not to be used with this drug or with carbon tetrachloride (see below) for it increases the toxicity of both.

Carbon Tetrachloride.—This drug is tasteless and very effective. In Egypt, Tomb and Helmy (1933) had only 19 deaths among 1,600,000 treated patients, and they said that most of these could have been prevented. Carbon tetrachloride is given in the same dose and by the same methods as tetrachlorethylene (see above). Pregnancy is not a contraindication to the use of the drug,

which is probably true of tetrachlorethylene also, though the fact has not been definitely established so far as I am aware.

Oil of Chenopodium.—This drug is given mixed with a dose of castor oil appropriate to the patient's age, which seems definitely to lessen absorption and hence toxicity. Mukerji and Ghosh (1943) found that oil of chenopodium deteriorates markedly upon standing whether kept in the dark or in the light. Dosage is 1.5 to 2 cc. for the adult, and the following (Darling) for children:

Age	*Dose in cc.*
4	0.2
6	0.3
8	0.4
10	0.6
12	0.7
13–14	0.8
15–16	1.0
17–18	1.25
19–20	1.5

Oil of chenopodium is also quite effective against roundworm, a matter of some importance, as indicated below. It has been given in millions of cases with only a few recorded deaths (Smillie said, in 1939, that he had had 22 deaths in over a million persons treated in Brazil) and even the number of instances of mild or moderately severe reactions is very small; nevertheless, it does have a higher toxicity than either tetrachlorethylene or carbon tetrachloride; it should not be repeated under two weeks. One should be especially cautious with it in poorly nourished individuals; in advanced cases of chronic cardiac or nephritic disease, in pregnancy, and in acute or chronic dysentery it is considered to be contraindicated.

Combinations of Anthelmintics.—Carbon tetrachloride has usually an undesirable effect upon roundworms, namely that of increasing their activity, with very serious results in some instances; but one can use oil of chenopodium in combination with either this drug or tetrachlorethylene when there is a mixed infestation with round- and hookworms. Brown (1934) said that the usual procedure under these circumstances is to give in one dose a mixture of 0.05 cc. of oil of chenopodium for each year of age up to twenty years and 0.1 cc. of tetrachlorethylene for each year of age, the adult dose being 1 cc. of oil of chenopodium plus 2 cc. of the other drug. One must be sure to follow this mixture with salts and not castor oil for the latter increases the toxicity of both tetrachlorethylene and carbon tetrachloride. Andrews (1942), preferring less potent agents, stated that when both roundworms and hookworms are present hexylresorcinol followed by tetrachlorethylene or several hexylresorcinol treatments in rapid succession will give most satisfactory results.

Thymol, Betanaphthol, Hexylresorcinol.—Thymol, the classical drug in mass attacks upon the disease, has now been superseded by the drugs discussed above; it was no more effective and was both more toxic and more expensive. Betanaphthol never made much place for itself because it was both toxic and ineffective. Hexylresorcinol has the advantage, above pointed out, of ridding the patient of both round- and hookworms, but, according to Brown (1934), it requires two treatments with this drug to accomplish what tetrachlorethylene will do in one so far as the hookworm alone is concerned. Smillie (1939) felt that the chief objection to hexylresorcinol was that it was too expensive for mass employment.

Iron Therapy.—There is only so much iron in the body and most of it is in the circulating hemoglobin. If the hookworm infestation has been overwhelmingly heavy, or if of only moderate degree but has persisted for a long time, the loss of circulating iron will be so great that the storage depots will have been seriously depleted by the time the patient is freed of the worms by the use of anthelmintic drugs. Under such circumstances recovery will not be rapid unless vigorous iron therapy is employed. Payne and Payne (1940), whose studies in Puerto Rico supplemented the earlier and well-known work of Rhoades *et al.* (1934), showed that following anthelmintic treatment alone it required one to two years for hemoglobin values to reach a satisfactory level but that the supplementary use of iron much improved the picture—facts which have been empirically known for a long time of course in all lands with heavy hookworm infestation.

THE TOXICOLOGY OF VERMIFUGES

Aspidium.—The milder symptoms consist in colic, diarrhea, headache, dizziness, dyspnea and yellow vision. Any one or all of these symptoms are not infrequently seen in slight degree, but more serious manifestations of poisoning, such as violent muscle cramps, jaundice, evidences of renal injury, blindness, delirium, convulsions and coma are very unusual; death is rare.

The stomach should be emptied by the use of a nondepressing emetic, such as powdered mustard (a teaspoonful in a cup of lukewarm water), copper sulfate (4 grains, or 0.25 Gm., in water), or zinc sulfate (15 to 30 grains, or 1 to 2 Gm., in water). A full dose of magnesium sulfate, 1 to 1½ ounces (32 to 48 Gm.), should be given to flush out the bowel. The patient may be stimulated by heat, strychnine, caffeine, digitalis, etc., as indicated by the symptoms. Recovery is slow.

Pepo.—The toxicology is unimportant.

Pomegranate.—The toxicology is unimportant.

Pelletierine Tannate.—Mild toxic symptoms, which are frequent, consist in dimness of vision, dizziness, muscle cramps, formication, weakness and trembling. Overdoses cause partial blindness with dilated pupils in addition to the above symptoms in aggravated form; there is also violent headache, vomiting and diarrhea, sometimes convulsions.

The treatment is the same as for poisoning with aspidium, but when an overdose of pelletierine has been taken one should proceed very cautiously as these patients are profoundly prostrated.

Santonin.—Overdoses of this drug cause early vomiting, abdominal cramps and sometimes, but not always, diarrhea. The patient is dizzy and very weak and may complain of headache and painful urination; it is said that hematuria may also occur. In severe cases there is an astonishing fall in temperature and the patient may go into violent convulsions; coma usually precedes death.

The treatment is the same as for poisoning with pelletierine. Every attempt must be made to keep the patient warm, and all available stimulants may be tried. An anesthetic, carried only to a light stage of relaxation, will control the convulsions, but if the patient sinks into coma he is almost certain to die.

Yellow vision often occurs in the routine use of the drug but is of no importance if unaccompanied by other symptoms.

Thymol.—Barnes, whose experience with thymol in the International Health Board campaigns was very extensive, wrote that the majority of patients treated with the drug showed some signs of its toxic action, such as flushed face, slight dizziness and drowsiness. Very rarely more serious symptoms appeared: vomiting and gastro-intestinal pain, severe vertigo, headache, tinnitus, visual disturbances, and cyanosis and collapse. There were very few reported deaths.

The treatment is the same as for poisoning with aspidium. *Alcoholic stimulants must not be used.*

Betanaphthol.—Smillie described 4 cases of poisoning in 79 patients treated with large doses of this drug. "The toxic action of betanaphthol in these 4 cases was a destruction of the red blood cells. The drug selected the red blood cells and destroyed them in great numbers, with resultant severe anemia, icterus, enlargement of the spleen and liver, enlargement of the gallbladder and hemoglobinuria. The white blood cells apparently were not destroyed by the drug. The liver, spleen, kidneys and other organs of the body were not affected primarily, but were markedly affected secondarily, because of the anemia, and because of the injurious effects produced by the elimination of large numbers of destroyed red blood cells." One of the patients had no subjective symptoms whatever, and another complained only of thirst and a slight weakness. The other two were very ill; there were nausea, vomiting and diarrhea, headache, exquisite tenderness in the regions of the spleen and gallbladder, a rise in temperature, pulse and respirations, and profound prostration. Both patients recovered.

The treatment consists in promoting elimination and providing stimulation as in the treatment of aspidium poisoning. Blood transfusion would seem to be indicated.

Oil of Chenopodium.—The symptoms of chenopodium poisoning are referable to the central nervous system and consist in nausea and vomiting, dizziness, internal ear deafness, tingling of the hands and feet, muscular incoordination and semicoma. The kidneys are also affected as is shown by albuminuria and the appearance of casts.

The treatment is similar to that employed in combating aspidium poisoning. In laboratory experiments, Salant found digitalis especially valuable as a stimulant. To combat the renal irritation, Darling advised the administration of hypotonic salt solution by the Murphy drip.

Carbon Tetrachloride.—Any one, or a combination of several, of the following factors is believed to account for the rare deaths from this drug.

Alcohol.—The drug is extremely toxic for chronic alcoholics and for those who drink alcohol immediately after treatment: violent vomiting, bleeding into gastro-intestinal tract, severe jaundice after forty-eight hours, urine scanty and highly bile-stained.

Roundworm.—The drug may so greatly stimulate ascarids that writhing masses of these worms can be seen through the abdominal wall. Pharyngeal and intestinal obstruction has been brought about in this way.

Food.—If the drug is not taken on an empty stomach, and if food, especially fatty food, is taken too soon after taking the dose, toxicity is greatly increased. Mackie (1939) felt also that the diet for two or three days prior to administration of the drug should be low in meat as well as in fat.

Calcium.—Lamson, Minot and Robbins showed that the tendency of the drug to cause acute central necrosis of the liver is greatly increased by calcium

lack. Since such lack is rarely seen except in poorly nourished individuals, all such patients should have their weight improved and the calcium supply restored before using carbon tetrachloride in them.

As a result of his experience in the treatment of 2 cases of acute poisoning, Allison (1942) offered the following outline of treatment which I have abbreviated somewhat: (*a*) Lavage the stomach and irrigate the colon (parenthetically I would remark that the use of oil, whether mineral or vegetable, for lavaging might be advantageous since carbon tetrachloride is very soluble in oil). (*b*) Force fluids by mouth and intravenously. (*c*) Administer hypertonic dextrose solution intravenously two to four times daily and 10 to 15 cc. of 10 per cent calcium gluconate solution by the same route every five or six hours for the first two days, then two to four times daily depending on severity. (*d*) Give a high carbohydrate, low fat and low protein diet and 20 grains of calcium gluconate by mouth every four hours. (*e*) Transfuse with blood or plasma as indicated and maintain in bed until evidences of liver and kidney damage have disappeared.

An interesting therapeutic approach in cases of acute poisoning was made by Beattie *et al.* (1944), who based their treatment upon the belief that the intimate cause of liver disturbance induced by carbon tetrachloride is an abnormal metabolism of methionine and related compounds. To a patient who had swallowed accidentally 30 to 40 cc. of carbon tetrachloride they gave 2 Gm. of *dl*-methionine by mouth, three hours later 1 cc. of a casein-digest-methionine solution by vein, after a short time 5 cc. more of this solution, and then finally continuous infusion of the same by drip apparatus at the rate of about 2 cc. per minute. The infusion was stopped after three hours when 436 cc. had been introduced and the next day the liver was no longer tender and the edge had much receded. On the next day, however, it enlarged again and the patient was given 2 Gm. of methionine by mouth in the morning and another 2 Gm. in the evening; on the next day the liver had again retracted; no more amino acid therapy was given and the patient recovered.

Tetrachlorethylene.—No serious toxic symptoms have been reported, except for 2 instances recorded by Sandground (1941) in which the patients were said to have gone into coma lasting several hours. A few patients complain of transient dizziness and giddiness.

Hexylresorcinol.—No systemic reactions of a serious nature have been recorded.

Gentian Violet.—The symptoms induced by this drug are principally gastrointestinal and, as recorded under Pinworm, quickly subside; contraindications are given in the same article. I have seen no report of serious systemic poisoning from this drug used as an anthelmintic.

ALLERGIC DISTURBANCES

HAY FEVER

The common, or seasonal, type of hay fever is that which begins every year when the particular pollen by which it is caused begins to be wind-borne, and persists until pollination ceases. The quite accurately predictable date of initiation of the annual attack, which used very often to bring down upon the heads of the victims of this disease the charge of being hysteriacs, is now known to be due to the fact that the flora of a given region pollinates with astonishing regularity under ordinary conditions; one should not overlook the fact, however, that unusual weather conditions can affect pollen production very significantly. The pollens of the common trees, grasses and ragweeds are the most usual offenders, conferring, respectively, the titles "spring," "summer" and "fall" hay fever. The symptoms are itching and congestion of the eyes, violent paroxysms of sneezing and a thin irritating discharge from the nose, often very profuse; oftentimes there is also itching inside the mouth, and "behind the eyes." The symptoms vary a great deal in severity during the day, being usually worst in the morning. In most cases there are "good" days and "bad" days, though very many sufferers are more or less incapacitated for active participation in affairs throughout the entire "season." Some of the patients experience asthmatic attacks in conjunction with their hay fever. Those who are affected by the ragweeds can entirely escape their attack by annual migration to a region where the wind does not contain these pollens, but escape for spring and summer sufferers is to be had usually only at sea, since the offending trees and grasses are quite ubiquitous upon the land. Perennial hay fever, the so-called "vasomotor rhinitis," is characterized by the persistence throughout the year of such symptoms as have been described above. Animal danders, vegetable powders, house dust, foods and drugs are held to be principally responsible for this type of the disease. The line between seasonal and perennial hay fever can be by no means always sharply drawn.

I believe that the earliest clear account of this disease was that of John Bostock, in London, in 1819. Abundant experience in War II is bearing out the observations of Clearkin (1943) and Cook and Kawasaki (1943) that hay fever had earlier been considered to be absent from the tropics and subtropics apparently only because it had not been looked for. The American Indian and the Negro are thought to be much less susceptible to the disease than the members of other races, at least in the western hemisphere.

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Specific Desensitization (Hyposensitization).—The practice of "desensitizing" hay fever patients by injecting them with increasing amounts of pollen extracts at short intervals during the several months preceding their annual attack was initiated by Noon, in 1911, and has since attained a considerable vogue, though the rationale of the procedure is not as yet entirely established. Perhaps the thermostable antibody of Loveless, which is demonstrable in the blood of all individuals suitably injected with antigens, offers the best avenue

of approach to an immunologic explanation of the occurrences that has yet been offered. In any case, however, as pointed out by Cohen (1944), the terms "desensitization" and "hyposensitization" are really not admissible in describing the phenomena since in treatment with a specific pollen antigen reduction in reagin does not actually occur; Cohen would have one merely speak of raising the patient's tolerance, leaving still open the question how this is brought about. Expert allergists, who prepare their own extracts and are able to give their full time and attention to the diagnostic and therapeutic study of their cases, are apparently able to effect a considerable degree of relief in many of their patients. Of course, the tendency towards enthusiasm is as apparent among the allergists as among those in other specialties in medicine, though Rackemann (1943) states that one feature is impressive in the reports from all clinics treating large numbers of patients, namely, that their percentage figures run about the same. The results, he says, are excellent in about 20 per cent of cases, good in another 60 per cent and poor in about 20 per cent. Specialists in this field are probably justifiably contending that all the cases should be handled by them; pending the realization of this utopian desideratum, however, I shall be obliged to continue to offer in these pages a brief outline of how the thing is done with such methods and means as the general man has at his disposal.

Methods of Testing Sensitivity.—(*a*) Scratch Test.—After cleansing with alcohol, the skin is scarified with a needle without drawing blood, a small quantity of the suspected protein is lightly rubbed in, and a drop of N/10 sodium hydroxide (4 Gm. NaOH to 100 cc. distilled water) is added. An urticarial wheal with pseudopods and an erythematous area is considered positive.

(*b*) Intradermal Test.—About 0.01 cc. of a liquid extract of the suspected substance is injected intradermally; this method is probably more clear cut and reliable than the previous one but the liability to constitutional reactions is greater.

(*c*) Patch Test.—A small area is washed and rubbed lightly with pumice stone; the suspected material, either in solution or rubbed into a paste, is placed on the area and covered with a small square of cellophane and held in place by adhesive plaster. The reading is after twenty-four hours or longer.

(*d*) Indirect Testing (Prausnitz-Küstner Technic).—One-tenth cubic centimeter of the patient's blood serum is injected intradermally in a normal arm, and twenty-four hours later the suspected substance is injected or scratched into this site; the usual urticarial wheal is a positive reaction.

The last two of these tests (patch and indirect) are being nowadays much employed in dermatologic practice.

Technic of Subcutaneous Desensitization.—Of the "standard" method, New and Nonofficial Remedies (1944) has this to say: "No uniform method of standardization has been adopted. Two methods are acceptable, first standardization by the nitrogen content of the extract, and second standardization by the amount of pollen or protein in the extract. The sensitivity of various patients is extremely variable so that the tolerance varies widely. For treatment graduated series of doses are supplied by the manufacturer. Most patients tolerate these standardized graduated doses, but in order to avoid untoward reactions at the beginning of the series, 0.02 cc. of the weakest solution should be injected intracutaneously before the series is begun. There should be no reaction or only a minimal wheal following this test."

Timing the Injections.—The usual practice in administering "preseasonal'

treatment is to give fifteen to twenty subcutaneous injections at intervals of once or twice weekly, the time of the last injection to coincide approximately with the beginning of the patient's "season," or either to antedate or postdate that time by a few days. Of course the immunity conferred by these injections, when successful, is only sufficient to carry the patient through his "season" in the vast majority of instances, and even then only if the "season" is a short one; the whole course of treatments must be gone through with again during the next year. A very important question from the patient's standpoint is how many years he shall have to continue faithful to the routine; *i.e.*, granting that hay fever untreated will diminish as he grows older and finally cease to plague him at all, to what extent will annual desensitizations hasten the malady's end? Some years ago Walker reported presumably permanent cures in 8 per cent of those treated for only one year and in 65 per cent of those treated for five years; I think that even now few observers are quite so sanguine.

Currently, it is the practice of some allergists to continue the treatment throughout the season, the usual attempt being to use the maximum dose reached before the season at weekly intervals throughout the season. Apparently a few patients cannot tolerate this dosage, however, developing either pronounced local swelling or delayed minor systemic reactions, or they merely complain of much lassitude on the day following the injection; Cohen (1940) advised that for such patients the dose should be reduced a quarter, a third or a half. Golan and Sack (1942) concluded from their comparisons of two treated groups that little was to be gained by continuing the specific therapy during the pollen season.

Another form of treatment which many allergists are now favoring is known as the "perennial" type; *i.e.*, the persistence in the injections for as long apparently as the patient will cooperate. The interval at which these injections are given varies in different practices, but I think that Vaughan (1940) and Nelson (1940) very likely expressed the consensus in advocating two weeks as ideal. Constitutional reactions are of course not infrequent in this type of treatment unless it is highly individualized. Among recent writers Markow and Rosen (1942) and Stoesser (1942) had better results with perennial than with conventional preseasonal care.

When the patient does not present himself until his symptoms have begun, it appears that something can be accomplished through "coseasonal" treatment; *i.e.*, administering just as much treatment as the patient can stand, bearing in mind that he is being assailed by air-borne pollen simultaneously; usually injections are given at one- or two-day intervals with greatly reduced dosage. Under such circumstances, Freeman (1936), of London, sometimes resorts to "rush" treatment—*i.e.*, the patient is hospitalized and eight or more pollen doses are crammed into him daily in order to get the desensitization completed in about a week. Waldbott (1937) also reported the satisfactory use of this method in selected cases. It seems to me, however, that this "rush" method is not sufficiently free of hazards to justify the general practitioner in employing it.

Another variant in desensitization technic is that of Loveless (1944) in which patients whose responses to desensitization in previous years are well known are desensitized in a given year by the administration of short "booster" courses suited to their immunologic needs. Since in this type of therapy it is the intention to treat all patients as intensively as their tolerance permits, and

as this means that generalized reactions occur not infrequently, it seems to me that the method is not one suitable for employment by the general practitioner.

Spain (1943) is studying a gelatin pollen extract which is more slowly absorbed than the standard aqueous extract; he feels that it is especially useful for the treatment of patients so sensitive as to accept poorly the usual aqueous pollen therapy. Taub and Rubens (1942) have also demonstrated slower absorption from extracts in oil.

Oral pollen desensitization is suggested from time to time but it is still the opinion of the vast majority of leading allergists that it is inferior to the injection methods. Iliff and Gay (1942) have tabulated all of the findings previously reported in the literature and comment on their wide divergence. Hecht *et al.* (1944) studied absorption of pollen allergen from the gastrointestinal tract with results suggesting a relationship between gastric acidity and the absorption of the allergen; they have not suggested as yet a practical application of these observations.

Reactions.—It is generally agreed that an urticarial reaction, however slight, is a warning sign and dictates use of the same, or perhaps even a slightly reduced dose, at the next injection. If the patient is kept under observation for about half an hour after each injection there is little to fear since prompt subcutaneous injection of epinephrine will quickly control such local or constitutional reactions as are likely to take place during that time. One should never inject pollen extract without pulling back on the syringe plunger to make sure that a vein has not been entered. Duke introduced the method of mixing each dose of protein solution with the following, and injecting the whole: 0.15 cc. of a mixture of ephedrine (3 per cent), 2 parts, and epinephrine (1:1000), 1 part, plus 0.3 cc. physiologic saline. With this mixture, and by controlling the dissemination of the pollen by the application of a tourniquet above the site of injection, he greatly reduced the number and severity of reactions. Others have had a similar experience. There are three objections to the method, however: it is rather painful; the ephedrine-epinephrine mixture may make the patient quite "nervous"; and the frequent use of epinephrine in this way may make him less responsive to the drug when direly needed, as for the relief of an asthmatic attack. Rice (1934) has given a valuable description of his handling of a case in which a large overdose of pollen was given through mistake: (*a*) intense local burning called attention to the error; (*b*) a blood pressure cuff was quickly substituted for the tourniquet already in place, and epinephrine was injected surrounding the extract site; (*c*) during the next hour there was itching up the arm when the tourniquet was released at intervals for a few seconds at a time, and once violent hay fever symptoms necessitated the placing of a dose of epinephrine in the other arm below a second blood pressure cuff; (*d*) for the succeeding three hours the periods of pollen release varied from thirty seconds to one and one-half minutes, each being followed by release of epinephrine; (*e*) complete release was safely effected four hours after the initial injection, the arm remaining sore for two days but no further constitutional symptoms occurring; (*f*) treatment was resumed after three days.

Nonspecific Proteins.—Nonspecific proteins, usually peptone, are much used in certain of the European centers, but in North America the results have not been comparable with those obtainable by use of the specific pollen substances. The method is described under Asthma.

Calcium, Viosterol and Ascorbic Acid.—In recent years it has been both affirmed and denied that there is calcium deficiency in allergy, and equally it

has been stated that calcium is and is not effective in treatment. Under such circumstances one is probably best advised to give the element a very minor place among the remedial agents in hay fever.

Rappaport (1934) and his associates showed that pollen injections and viosterol treatment combined are capable of producing somewhat better results than either alone, but they employed much higher viosterol than most men would care to use. Crandall and Feinberg (1934) gave thirty drops of viosterol daily to a series of patients without effect.

Holmes and Alexander (1942) reported favorable results with the use of high ascorbic acid dosage, but Hebald (1944) and Engelsher (1944) were unable to confirm these findings.

Histaminase and Histamine.—Several investigators have long held that the release of histamine or a histamine-like substance in the body, or the abnormal response of the body to the presence of histamine, may be directly responsible for the symptoms in the various types of allergy. Therefore, when it was discovered a few years ago that the enzyme histaminase exists in the body and is capable of inactivating histamine, clinical trials of this histaminase began to be made in many types of allergic patients. To date, however, despite a few encouraging reports such as that of Roth and Horton (1940), who used the drug in various types of allergy with success in some instances, the majority of the reports have certainly been unfavorable; for example, Miller and Piness (1940) failed to obtain unequivocal evidence of the drug's value in their 42 cases, Frank and Harris (1940) failed completely in their 20 cases, Keeney (1940) in his 15 cases, and Peshkin *et al.* (1943) in their 48 cases. Knoll and Beinhauer (1940) obtained pronounced improvement in about one third of their 101 cases but their own analysis shows that more than half their markedly improved patients were afflicted with atrophic dermatitis or acute urticaria, both of which are given to spontaneous regression and even complete involution. Decidedly, therefore, it seems to me that a clear case has not yet been made out for histaminase, but since its toxic effects are practically negligible and its methods of administration simple, further studies would seem to be desirable. Histaminase is taken orally in enteric-coated tablets in average dosage of 60 to 75 mg. daily.

The employment of histamine itself is discussed under Asthma.

Ephedrine, Neosynephrine, Propadrine.—The use of these drugs systemically in asthma and hay fever is discussed in Asthma.

Nitrohydrochloric Acid.—Some years ago I revived the use of nitrohydrochloric acid by mouth. Widely scattered practitioners still continue to report to me that they oftentimes obtain startlingly good results with this simple agent; of course, the larger proportion of completely negative results is never reported to me. Rackemann (1944) says he sometimes uses this treatment with success in asthma. The following prescription and the method of using it are worth bearing in mind and trying upon occasion.

℞	Nitrohydrochloric acid (*not* the dilute)	ʒivss	18.0
	Distilled water to make	℥iv	120.0

The patient is directed to take 1 teaspoonful of this in ⅔ glass of water, followed by another glass of water, after each meal and again upon retiring (as near midnight as possible). This is a pleasantly acid but not corrosive tasting mixture, which may be dispensed in the usual bottle with a cork stopper. The midnight dose is very important; when it is omitted the patient will

almost invariably have early morning symptoms. The ingestion of the acid, even in this large dose, cannot be looked upon as in any sense dangerous, though to protect oneself against the charge twenty years later of having ruined the patient's teeth it may be advisable to have it taken through a glass tube. Another precaution should also be taken: namely, that of forbiddind the use of any laxatives or purgatives not prescribed, for there is perhaps some very slight danger of calomel being converted into the bichloride of mercury by the acid. The use of the remedy is begun only with the onset of the individual's hay fever season.

Potassium Chloride.—Several years ago, Bloom (1938) reported striking benefit in 29 cases of hay fever treated with this drug by mouth. Rusk *et al.* (1939), Smith and Steffensen (1940) and Parker (1940) have also reported successful treatment in a sufficient proportion of their cases of allergies of various types to keep up one's interest in the drug. But the reports of all the specialists in allergy have been almost completely unfavorable: Harley (1939); Harsh and Donovan (1940); Rubin *et al.* (1940); Miller and Piness (1940); Spain *et al.* (1940); Furstenberg and Gay (1940); Engelsher (1940). Recently, however, Stoesser (1942) has obtained sufficient evidence of benefit with the agent in children to warrant further investigation.

Bloom recommended that a 5-grain (0.3 Gm.) powder of potassium chloride be dissolved in a glass of water and that 3 or 4 such doses be taken daily; insistence upon dilution before taking is necessary in order to avoid severe gastric irritation. Parker prescribed the drug in a solution containing 5 grains to the teaspoonful, which was then much diluted with water before taking; he also used potassium gluconate tablets, giving a dosage three times as great to compensate for the lower potassium content of this salt. Bloom (1939) says that when properly given the drug only rarely produces side effects, the most important being occasional aggravation of asthma, which calls for immediate cessation of treatment; other rare effects are nausea, diarrhea and urinary urgency.

Endocrine.—Although endocrine therapy is on the whole usually quite unsatisfactory, it has sometimes been directly responsible for the disappearance of allergic symptoms. The coincidence of one of the classical endocrinopathies is the indication for its use, not promiscuously in allergy *per se*.

Surgery.—Despite the allegations of those who hold out for surgery in all conditions, I believe it is now the consensus among otolaryngologists that little, if anything, is to be hoped for from operative procedures in the treatment of hay fever.

Topical Applications.—The application of a cocaine solution to the mucous membranes of the nose several times during the day will give considerable relief in many cases, but the remedy is absolutely contraindicated as a routine procedure for very obvious reasons. Butyn or alypin is sometimes very well substituted, 1 or 2 grains to the ounce (0.06 or 0.12 to 30 cc.) in solution; the latter may be used in alkaline medium. The use of a dilute solution of epinephrine as a nasal spray is often unsatisfactory for two reasons: first, it is in itself sometimes very irritating when used under these conditions; and second, the patient often experiences an attack of hay fever of explosive violence when coming out from under the brief influence of this drug.

The following is Duke's prescription for an epinephrine mixture:

℞	Solution epinephrine hydrochloride (1 : 1000)	1.0 cc.
	Dilute acetic acid	0.3 "
	Resorcin solution (3 per cent) to make	32.0 "
	Label: Apply to conjunctiva and nasal mucosa when necessary.	

Ephedrine hydrochloride or sulfate, used in a 1 to 3 per cent aqueous solution, is relatively free from the objectionable features of epinephrine's action and is effective for a much longer time. Neosynephrin is used in 0.25 per cent solution and in many instances with good success, often without disagreeable by-effects.

Ionization (Iontophoresis).—The impregnation of the nasal mucosa with zinc ions, through dissociation of a zinc sulfate solution by galvanic current, was revived some years ago in both England and the United States and a description of the method was included in earlier editions of the book; such description is omitted from this edition of the book for the reason that reactions both during and after the treatments are often quite severe and convincing evidence of the efficacy of this sort of treatment has not been produced.

Pollen Filters and Air Conditioning.—There seems to be no doubt that hay fever sufferers are greatly, sometimes completely, relieved during their sojourn in a room which is "air conditioned"; in more severe cases some one or other of the several types of filters which will completely remove the pollen from a room may be needed. Such equipment is relatively expensive of course and usually requires considerable care to be maintained in satisfactory operation. The provision of an adequate number of pollen-free rooms in hospitals, without excessive charge for their occupancy, would be a great boon to many sufferers.

Masks.—Nowadays one occasionally encounters an individual on the street wearing a mask covering the mouth and nose. I know of no controlled study of the efficacy of such masks but should think it would be difficult to prevent leaks between them and the skin and that furthermore sufficient pollen might enter through the unshielded eyes to induce symptoms in some instances.

ASTHMA

The asthmatic is one who is prone to attacks of difficult breathing, the immediate cause of which has been known, since its first mention by Floyer (1648), to be spasm of the bronchial muscles plus edema of the bronchial mucous membranes; latterly, Steinberg (1932) has shown that bronchial occlusion due to mucous gland secretion is of importance also. But the fundamental cause of these spasms still remains unknown, though many of the cases rest upon an allergic basis. The attacks may last for a few minutes to several hours and are very distressing, though death from asthma *per se* is unusual—that is, if we speak only of extrinsic (allergic) asthma, for Rackemann (1940) has reported a mortality of 8 per cent in a group of 283 patients with the intrinsic type (see below). Characteristically, the patient coughs at the end of each attack and raises sputum which contains Charcot-Leyden crystals and the bodies known as Curschmann's spirals. These attacks may be infrequent or they may occur every day or several times during the night over a long period. Osgood (1943) finds that the degree of systolic blood pressure fluctuations occurring synchronously with the respiration offers an approximate indication of the degree of respiratory obstruction present; Rackemann (1944) finds these fluctuations occurring more frequently in older persons who have emphysema. In simple uncomplicated asthma relaxation is usually complete between

spasms, but most long-standing cases are complicated by emphysema and chronic bronchitis and are therefore "wheezy" and somewhat distressed at all times. Unless complicated by the two diseases just mentioned, pain in the chest and cyanosis are rare during attacks. Just as we had settled down comfortably in the belief that "cardiac asthma" is always a state characterized by the mere coincidental occurrence of asthma and cardiovascular disease, Craige (1941) analyzes seven asthmatic deaths and finds it not unreasonable to conclude that, at least in severe status asthmaticus, signs of right ventricular failure may sometimes appear and be due entirely to extracardiac factors; the findings of Schiller *et al.* (1943) are confirmatory. Subcutaneous pneumothorax or spontaneous pneumothorax is a very rare complication. A number of observers have stated that there is a tendency toward hypoglycemia in asthma and Abrahamson (1941) points out that the concept of hyperinsulinism underlying asthma offers an explanation for the frequency of nocturnal attacks; but upon the other hand, Goltman (1942) feels that diabetes may be associated with asthma much more frequently than has been suspected. Tocker and Davidson (1944) find that asthma improves during the period of activity of a tuberculous process. It would seem that the asthmatic who develops the disease after the age of forty, particularly if it is of the intrinsic type (see below) is the individual most likely to die therefrom; periarteritis nodosa sometimes occurs as a complication in these cases. Gaarde *et al.* (1942) found that about 14 per cent of a consecutive series of 189 cases of asthma, nearly equally distributed between the two types, developed significant pulmonary complications when they were subjected to major surgical procedures.

It is commonly held that asthma is a rare disease in American Indians, but Derbes and Engelhardt (1943) find it certainly not an uncommon disease in the Negro. Cook and Kawasaki (1943) find asthma a frequently encountered and often quite severe disease in the semitropical Hawaiian area, and Leopold (1945), studying 200 soldiers returned with asthma from overseas locations during War II, concluded that a climate of high humidity with frequent rain can be a significant factor in the onset and continuation of chronic perennial bronchial asthma.

THERAPY

When it first became apparent that asthma could best be studied upon an allergic basis, it was felt by investigators that it would ultimately become possible to desensitize and thus cure all persons suffering from the disease; however, this enthusiasm has now considerably waned, and it is frankly admitted by conservative students of the subject that there is need for more than one type of therapeutic approach to the disease. As a result, it has become possible to classify the cases as "extrinsic," "intrinsic" and "miscellaneous unclassified" asthma. The extrinsic cases are those that are believed to be caused by hypersensitiveness to some foreign substance outside the body, the sufferers having asthma on exposure to or contact with it; *i.e.*, these are the cases of true allergic asthma. Pollens, animal danders, dusts, foods, fungi and a great variety of other substances are the offending agents. The intrinsic group comprises cases that are believed to be due to infection in the upper or lower respiratory tract, cases that are reflexly caused by bad teeth, nose and throat pathology, constipation, cholecystitis, or other well-defined foci of infection, and cases more or less directly associated with such conditions as pregnancy, obesity, nervousness and bad hygiene (the latter to include such items as an

unwise dietary schedule, a lack of proper fresh air and exercise, insufficient intake of fluids and continued overwork without proper rest periods). The miscellaneous unclassified cases are, of course, just what the name implies. In the extrinsic group, treatment consists in attempting to find the offending substance and eliminate it from the environment, perhaps by removing an animal, such as a cat or horse, or deleting a certain type of food from the dietary, or by removing an article, such as the feather pillow or a substance met with in the occupation, or by a more radical procedure, such as a change of climate, residence, or work. Where these methods fail, or seem impracticable, attempt is made to desensitize by injection as in hay fever. In the intrinsic group, attempt is made to remove foci of infection, to build up resistance by the employment of bacterial vaccines and to correct the pathologic condition of mind or body which is believed to be responsible for the asthmatic state.

The results attained in the treatment of asthma are extremely variable, but conservative investigators of the disease are in agreement that if the achievement of absolute cure is the only indicator of the efficacy of the treatment program, a picture is presented which is tinted much too darkly to represent the whole truth, since a large number of patients can be greatly relieved though they may never be cured in the fullest sense of the term.

Specific Desensitization (Hyposensitization).—When indicated, this type of therapy is instituted just as in the treatment of hay fever; it is generally conceded, however, to be less effective in asthma than in hay fever.

Bacterial Vaccines.—Some years ago a number of authors were able to report results with bacterial vaccines that were quite comparable with those obtained by the institution of specific desensitization. The usual method was to prepare vaccines from pure cultures of organisms obtained from the thick mucus coughed up from the lungs during the breaking-up of an attack. In recent years there has been little in the literature regarding this method of treatment save the general statement, frequently encountered, that "bacterial vaccines are of little if any value." In 1939, however, Stevens and Crump independently studied the use of vaccines in asthmatic children and felt that some good results were obtained in these young patients. Crump prepared her vaccine from material removed through the bronchoscope. Cooke (1943) employs autogenous vaccine in selected cases but recognizes that too large dosage may induce a severe status asthmaticus.

Nonspecific Proteins.—Some observers believe that there is a nonspecific factor of considerable importance in specific desensitization, calling to witness the fact that relief is often obtained without much alteration in the skin test. Pagniez and Widal, Abrami and Brissaud, Auld, Schiff, Urbach and others have reported the use of peptone. Van Leeuwen, Maxwell and others claimed success with tuberculin. A number of observers have used injections of milk; Nelson and Porter media broth; Van Leeuwen, and Nelson and Duckworth, sulfur; autohemotherapy has had a trial. All have reported more or less success, but there is no lack of dissentient or at least healthily skeptical voices: Ramirez, Behrman, Irons. Despite the fact that the advocates of this kind of treatment seemed for a time to have become almost fanatical about it, I find no significant references to the matter in the very recent literature.

Peptone.—Schiff prepares a 33 per cent solution in glycerin and water by rubbing Armour's peptone siccum (dry) in the mixture of the other two ingredients, warming to complete solution, and then filtering until clear. This

solution may be sterilized and will keep at room temperature. Three minims is a safe initial dose, increased by 1 minim at biweekly or triweekly intervals up to 1 cc. Auld sometimes modifies the mixture as follows: to 1 ounce (30 cc.) of serum, pipetted off the patient's blood drawn from the arm on the day before, is added 1.5 Gm. of Armour's No. 2 peptone, 0.006 Gm. agar which has been well boiled, and about 10 drops of chloroform; the mixture is incubated at 37° to 40° C. for three hours and the clear fluid pipetted off for use the next day. Very slow intravenous injections of this fluid are given twice a week, beginning with about 10 minims (0.6 cc.) and increasing 5 minims (0.3 cc.) each injection until 45 minims (3 cc.) is reached, or continuing at any time with the dose which gives greatest relief. At the time of his last report to come to my attention, Urbach was giving much of his peptone by mouth.

Whole Blood (*Autohemotherapy*).—From 5 to 10 cc. of blood is withdrawn from the arm vein and immediately reintroduced intramuscularly into the buttock; injections twice or oftener per week, usually not exceeding a maximum of 20 cc. per dose.

Milk.—Straight whole milk is poured into a 2-ounce (60 cc.) rubber-capped bottle, stood in a water bath up to the neck of the bottle and boiled for one hour. Initial dose of 0.5 to 1 cc. is increased by 0.5 cc. at triweekly intervals up to 2 or at most 3 cc.; the injections are usually given subcutaneously.

Tuberculin.—Old tuberculin is used in dilutions of 1 in 1,000,000; 1 in 100,000; 1 in 10,000; 1 in 1000; and 1 in 100 (rarely). The first dose of 0.1 cc. of the 1:1,000,000 is increased at weekly intervals to 0.2, 0.4, and 0.6 cc., after which the next dose is 0.1 cc. of the next dilution, and so on. When the 1:1000 dilution is reached, some men make a practice of increasing the interval to two weeks and the dose by 0.1 cc. until 0.5 cc. is reached; this dose is repeated monthly as long as necessary.

Broth.—A standard broth such as that used in making artificial culture media is employed in dilutions and dosage much the same as tuberculin.

Sulfur.—Nelson and Duckworth (1934) used colloidal sulfur in doses of 0.5 cc. of 1:10,000 to 1 cc. of 1:1000.

Gold Sodium Thiosulfate (*Sanocrysin*).—The reports are by no means convincing that this drug is of value in asthma, and its use is always fraught with danger.

Histamine and Histaminase.—Histamine has been used in various allergic affections for a number of years throughout the world, but there has not been agreement regarding its efficacy. In this country Thiberge, in 1935, made the astonishing claim of improvement in 95 per cent of his treated asthmatics. More recently, Farmer (1941) has reported more conservatively on 23 patients who had either asthma of the "intrinsic" type, or vasomotor rhinitis, or both; his results were sufficiently encouraging to warrant his continuing the study. Farmer began with a subcutaneous injection of 0.00001 to 0.0001 mg. (0.01 to 0.1 gamma) of histamine phosphate, giving 2 or 3 injections weekly in the beginning and increasing the dose 50 per cent each time; later the injections were spaced at five-, seven-, ten-, fourteen- and twenty-one-day intervals, depending upon the patient's tolerance and the results achieved; the maximum doses, not often employed, were 50 to 75 gamma. The precautions to be taken are the same as in specific desensitization, but systemic reactions have occurred very rarely. Recently, Gant *et al.* (1943), of the Allergy Clinic of the Massachusetts General Hospital, have reported surprisingly good results with histamine taken by mouth in vasomotor rhinitis. They start with a 1:1000

dilution and a dose of 1 drop in a glass of water, increasing the dose 1 drop each day until the toxic effects appear; thereafter the patient is maintained on the dose just below the toxic one, repeating his dose as often as is necessary to control the symptoms, but preferably when the stomach is empty.

The work with histaminase is considered under Hay Fever.

Calcium, Viosterol, Ascorbic Acid, Endocrines, Pollen Filters and Air-conditioning, Face Masks, Nitrohydrochloric Acid, Potassium Chloride.—All these measures have been discussed under Hay Fever.

Iodides.—The use of iodides as adjuvants in the treatment of asthma seems to be of such general acceptance that recent medical literature reveals no special studies of their efficacy. The employment of sodium and potassium iodide probably finds its rationale in the well-known ability of these salts to increase exudation from the respiratory mucous membranes and to liquefy mucus. Many practitioners feel that the administration of small doses of potassium iodide over a long period of time definitely prolongs the interval between spasmodic attacks. Cooke (1943) says that occasionally "it works marvels" in dosage of 5 to 10 grains (0.3 to 0.6 gm.) three times daily. The following prescription has been recently proposed (J.A.M.A. 124, 200, 1944):

℞	Apomorphine hydrochloride	gr. ii	0.13
	Potassium iodide	ʒv	20.00
	Syrup of wild cherry to make	℥iv	120.00
	Label: 1 teaspoonful (5 cc.) every 4 hours.		

The intravenous administration of 10 per cent solution of sodium iodide in doses up to 10 cc. has been tried, but it is doubtful if this is superior to the oral method except in a few patients in whom massive doses of iodides by mouth cause excessive iodism. Some patients, however, are equally intolerant to the intravenous medication; the concentration of iodides in blood and spinal fluid seems to be about the same when given by either route. The Council on Pharmacy and Chemistry (1944) holds that the intravenous injection of sodium iodide is a dangerous procedure and should not be employed except in severe paroxysms of asthma. Cleveland (1934) has reminded us that iodism may occur in asthma patients taking proprietary or patent medicines containing iodides, perhaps unknown to their attending physician.

Epinephrine (Adrenalin; Suprarenalin; Suprarenin).—It is often tersely stated that a subcutaneous injection of epinephrine will relieve any attack of asthma, but this statement, like so many categorical pronouncements, can be accepted only with certain reservations with regard to dosage and tolerance. The usual practice when attempting to relieve an attack with the drug is to give subcutaneously 0.5 cc. of 1:1000 solution, repeating after a few minutes if relief has not been obtained and tremor has not occurred. But Sterling (1940) and many other allergists are opposed to this as a dangerous practice; Sterling says that maximal therapeutic effects can be obtained with much greater safety with a dose of 0.1 to 0.15 cc. repeated at intervals of thirty minutes for 2 or 3 doses if necessary. The amount required to control subsequent attacks varies greatly with individuals but is usually less than used in the first instance. The custom nowadays is to teach patients to administer the injections themselves in the attempt to forestall attacks; such individuals can usually assure themselves a comfortable night by the injection of a few drops in the evening—in the beginning, that is, but as time goes on they nearly always require larger and larger doses. This is true drug tolerance but there

is no such thing as addiction in the opium-addiction sense, though Lawson's admonition is worth heeding when he points out the psychic dependence upon the drug in several of his patients. Following the animal experiments of Luckhardt and Koppanyi, a number of years ago, a few men reported that massage of the site of injection of epinephrine one-half to several hours later causes the typical effect to be manifested again to a diminished extent, but subsequently most observers have failed to confirm this clinical finding.

Epinephrine should be given intravenously (well diluted!) in asthma only under circumstances of direst necessity. Despite the fact that many allergists demur, it seems to me that the drug if not absolutely contraindicated should at least be used with utmost caution in advanced arteriosclerosis or if there is greatly elevated blood pressure. A case of subarachnoid hemorrhage (Flexner and Schneider, 1938) and one of hemiplegia (Keeney, 1939) in individuals with normal blood pressure are on record. Further contraindications are hyperthyroidism, cardiac dilatation, and coronary disease; pregnancy *per se* does not contraindicate the use of the drug.

Rackemann states that in the treatment of children especially, dry epinephrine (1.5 mg.) placed under the tongue is frequently efficacious. As a result of the studies of Graeser and Rowe (1935–1939) the use of epinephrine by inhalation, with absorption occurring in the lungs, has become popular as a means of enabling the patient to self-administer the drug. Motor-driven nebulizers are available but the more usual practice is merely to employ a glass atomizer with a hand bulb, selecting carefully one capable of delivering a fine "nebulized" spray. The Council-accepted 1:100 solution (specially prepared for this purpose and under no circumstances to be used for injection) is employed. Dosage must of course be determined by each patient; great caution must be enjoined in the beginning for a few extra squeezes of the bulb may induce very disagreeable if not dangerous symptoms of excessive epinephrine action. Westcott and Gillson (1943) find hypodermic injection of the ordinary epinephrine solution still effective after continuous use of inhalation therapy. Richards (1940) modified the method through replacing the hand bulb by a stream of oxygen from a tank; at a flow rate of 4 to 7 liters per minute, 1 cc. of solution is vaporized in three to ten minutes. Lockey (1943) finds that the addition of 5 per cent glycerin to the solution often prevents irritation and dryness of the throat.

In studies since 1938, Keeney has introduced "slow epinephrine." The Council-accepted (1944) preparation is a suspension of epinephrine base in vegetable oil, 1:500. The advantage of this preparation is that for many patients the action of the drug is prolonged and therefore injections do not have to be made so frequently. Usually recommended dosage is 1 cc. though the Council states the dosage as 0.2 to 1.5 cc.; Insley and Segaloff (1940) feel that initial adult dosage should never exceed 0.5 cc. Of course the contraindications and reactions of ordinary epinephrine apply to this preparation; unusual reactions have been reported in only a few instances but Rackemann (1943) says they not infrequently follow these injections: headache, nausea, vomiting, cyanosis, dyspnea, chills, perspiration, insomnia, extreme tremor, nervousness, vesicular urticaria, swelling and edema of the forearm. In most cases these symptoms have manifestly been due to merely excessively rapid absorption of epinephrine, but it is not certain that the oil in which the drug is suspended may not rarely cause an allergic reaction of its own. All who have experience with this preparation counsel that it is to be given intramuscularly

and not subcutaneously; one should be certain of not being in a blood vessel before injecting. Dorwart's (1940) experience, in which he was able to control the reaction to a great extent through the emergency application of a tourniquet to the arm and releasing only a few moments at a time, indicates the advisability of always injecting this preparation into the deltoid muscle and not into the buttock. In the beginning it was considered necessary to use only a dry sterilized syringe to prevent injecting oxidizing water into the stock bottle of the mixture, but now that single-dose commercial ampules are available, Keeney feels it unnecessary to observe this precaution.

Spain *et al.* (1939) introduced a 1:500 epinephrine-gelatin mixture for which they claimed effectiveness comparable to the above oil mixture and the additional advantage of nonantigenicity. Kalmon (1940) made a comparative study of the two mixtures on 22 patients with a total of 225 injections. In the end he preferred the oil mixture because it is less painful and irritating and gives a few hours' longer relief; the patients without exception preferred this mixture also. According to Rackemann (1943), however, Miller has employed the gelatin mixture in over 200 cases and found it "useful." The gelatin mixture must be kept in the refrigerator, while the oil mixture need not be. Since the gelatine mixture requires to be warmed to accomplish liquefaction, Abramson (1943) has been experimenting with the addition of sufficient urea to maintain the gel in the sol state at room temperature; it will be interesting to observe the outcome of these studies for all attempts to prepare mixtures permitting the slow and regular absorption of incorporated drugs are potentially of great importance.

Ephedrine.—In the treatment of asthma, ephedrine has certainly been shown by Althausen and Schumacher, Piness and Miller, Munns and Aldrich, Middleton and Chen, Thomas, and many others, to be (*a*) very much less reliable than epinephrine in either relieving or preventing the attacks; (*b*) when given by mouth, much slower (ten to thirty minutes) in exerting its effect than the older drug; (*c*) much longer lasting (often many hours) in its effects when they are obtained; (*d*) much more toxic. In severe cases it is usually very little if at all effective, and in moderately severe or mild cases the result seems to depend upon whether or not the patient happens to be susceptible to the drug's action, whereas practically all persons respond favorably to epinephrine. The chief advantages of ephedrine are that it can be given by mouth and that its effect is relatively long-lasting. The average dose is perhaps 25 to 55 mg., but it varies widely; some patients are able to prevent an attack by taking a small dose upon retiring, whereas many others are forced to take 50 to 100 mg. or more at intervals of several hours throughout the day in order to obtain any measure of relief. Brown (1940) very cleverly employs a capsule and an enteric-coated tablet together at bed-time, the effect of the tablet beginning just about when that of the capsule has ceased. Both the sulfate and hydrochloride (the asserted superiority of this salt is largely academic) are available commercially in a wide range of tablets, capsules, solutions, elixirs, syrups, and ampules for hypodermic administration. In Munns and Aldrich's experience with children, the minimum and maximum doses were 12 and 50 mg., respectively.

Many physicians have noted that the drug often becomes less and less effective with succeeding doses, but habit-formation or abstinence symptoms have never been reported to my knowledge. The chief objection to ephedrine is the frequency and oftentimes marked though not serious nature of its side-

actions, which preclude its use altogether in a large proportion of patients: nausea, vomiting, sweating, bladder irritability, urinary retention, skin eruptions, dysmenorrhea, palpitation, vertigo, tremor, general nervousness and apprehension, insomnia, and so on. Caffeine and nicotine in most instances definitely increase the severity of the symptoms. The greatest possible care should be exercised to avoid giving epinephrine and ephedrine in a way which might permit their effects to overlap. The barbiturates, especially amytal, are much used to counteract the ephedrine side-actions.

I do not find any evidences in the literature that racephedrine has any distinct advantages over the older drug.

Many observers have reported the successful use of ephedrine by mouth in hay fever, subject to the same qualifications as to dosage and undesirable side-effects that apply in asthma. Thommen's series comprised 245 patients, more than 70 per cent of whom obtained some measure of relief; 22 per cent could not use the drug at all because of its untoward effects.

Amphetamine (Benzedrine), Propadrine, Neosynephrin.—Swineford (1938) found that benzedrine inhalation was useful in the relief of mild and moderately severe asthmatic attacks, and that when used in conjunction with epinephrine or ephedrine it seemed to increase their efficacy; there were a few minor toxic reactions but sleeplessness was complained of following only 2 of the 69 attacks in which the drug was used.

Boyer (1938) was pleased with the relief obtained in all but 2 of the 44 patients to whom he gave propadrine hydrochloride at intervals of two hours or longer; the Council (1944) advises a dose of $\frac{3}{8}$ grain (0.024 gm.), but Boyer found it necessary to double this dose in many instances and was particularly struck with the absence of side effects as compared with ephedrine.

As an inhalant, Graeser (1939) found neosynephrin in 5 per cent solution of no value, but Richards *et al.* (1940), with their technic (see Epinephrine above), found it somewhat effective and free from side effects.

Theophylline Derivatives (Aminophylline and Theocin).—Effron, in 1936, stated that one could terminate asthmatic attacks of great severity by the intravenous administration of theophylline-ethylenediamine (aminophylline); he cautioned that a single drop under the skin may cause excruciating pain and also that the drug tends to sclerose veins. It is usually given in a dosage of 0.24 to 0.48 Gm., the amount of the solution injected depending upon which of the commercially available ampules is being used. Rackemann (1943) says that the larger are no more effective than the smaller doses, but Barach (1944) seems always to prefer the larger dose. Many men have reported favorable results with this drug; interestingly, Osgood and Ehret (1943) suggest that its principal action is by increasing the blood flow through the pulmonary circulation and that its bronchodilating effect is of secondary importance. Tuft (1936) found aminophylline of some value when given by mouth in combination with theobromine and caffeine. Brown (1940) uses a capsule containing $\frac{1}{2}$ grain (0.03 gm.) ephedrine sulfate, $\frac{1}{2}$ grain (0.03 gm.) sodium phenobarbital, and 3 grains (0.2 gm.) theophylline sodium acetate. Dees (1943) uses the drug in the form of rectal suppositories, finding that ordinarily two suppositories, one in the morning and one in the evening, suffice to keep the patient symptom-free during the entire day and night.

Occasionally there are reactions to aminophylline characterized by hyperpnea, a feeling of warmth and burning of the eyes, metallic taste, and nausea

and vomiting. Unger (1944) says he has never seen any dangerous reactions in the hundreds of injections he has given; Merrill (1944) reported 3 deaths but all the patients had heart disease.

Atropine.—As compared with epinephrine, atropine when used alone is the less valuable drug for two reasons: first, because most patients are not markedly relieved until doses large enough to cause flushing, considerable dryness of mucous membranes, and more or less cerebral excitement are used; and second, because the majority of patients become tolerant to it much sooner than they do to epinephrine. Cooke (1943) says that atropine and belladonna are contraindicated drugs.

Syrup of Ipecac.—Ratner (1942) considers this drug a very valuable agent when plugging of the bronchi is the cause of the prolonged attack. He says that if epinephrine is not giving the expected relief, ipecac will cause forceful vomiting with release of the plugs and relief so speedy as at times to be truly dramatic. To infants and young children he gives ½ to 1 teaspoonful (2.5 to 5.0 cc.) and if this does not cause vomiting he gives 2 teaspoonfuls (10.0 cc.). In older children and adults repeated doses may be given until the desired result is achieved. The ipecac is followed by warm water.

Morphine.—Because of the chronic nature of the disease this drug obviously cannot be used to relieve each of the severe attacks though it will often do so effectively. As a matter of fact, most leading allergists now consider even a single dose of the drug taboo under any circumstances, the reason being that morphine causes constriction of the bronchioles, diminution in tracheal ciliary movement and depression of the respiratory center; these actions have undoubtedly caused death in numerous asthmatic patients.

Anesthetics.—Maytum (1931) relieved extremely severe attacks, and Kahn (1935–1937) interrupted status asthmaticus, by the colonic administration of ether. Kahn, using equal parts of ether and olive oil, allows twenty minutes for the administration of 5 to 7 ounces (150 to 210 cc.) of the mixture to the average adult; no preliminary cleansing enema is given. For a child of five to nine years he gives 1½ to 2 ounces (45 to 60 cc.). Rackemann (1943) has satisfactorily instilled 60 cc. of the mixture two and even three times daily. Maietta (1942) made a preliminary report on the intramuscular injection of the contents of an ampule containing 1 cc. of ether and 1 cc. of peanut oil; in status asthmaticus such injections were made every four to six hours, and in another group of long-standing asthmatics injections once or twice weekly seemed to effect a reduction in the severity of the disease and to make other therapy more effective. Fuchs (1937), using avertin fluid, found a dose of 60 mg. usually adequate to induce relief; he states that once the crisis was overcome, some of his patients were free from symptoms for days and even weeks, and he also considers it noteworthy that refractoriness to epinephrine was lost.

Inhalants.—In mild cases the inhalation of the smoke from an ignited mixture of stramonium and a nitrate may be resorted to with advantage once or several times during the night; there is available a number of commercial asthma powders and cigarettes, but the following is more economical:

℞	Sodium nitrate	℥ss	15.0
	Powdered anise	℥ss	15.0
	Stramonium	℥j	30.0

Label: A teaspoonful to be ignited and the smoke inhaled.

Lippard (1939) is very skeptical of the value of these inhalants and thinks that perhaps patients are sometimes made worse by them. Steaming preparations, as described in Common Cold, are also sometimes used.

Acetylsalicylic acid-Whiskey.—Five to 10 grains (0.3–0.6 Gm.) of aspirin, administered together with a hot toddy, is a potent mixture which will oftentimes conquer even severe paroxysms (Duke, 1928). The first dose of the aspirin should be very small, however, because many asthmatics are hypersensitive (*i.e.*, have an allergic reaction) to the drug; indeed, most allergists show signs of distress at the mere mention of aspirin.

Physiotherapy and Breathing Exercises.—Various forms of hydrotherapy, baths, spa cures, ultraviolet and roentgen-ray exposures have been advocated from time to time, but none merits special description here. In hay fever, diathermy is sometimes applied locally to the nasal mucosa, or special quartz rods are used to carry ultraviolet rays to the anterior and posterior nares. Perhaps the best known of the several schemes for inducing forced expiration is that of Hofbauer, in Vienna. The thing seemed very complicated when I saw him demonstrate it, but this may be only the statement of a fact about myself; Livingstone and Gillespie were investigating the matter in England, in 1935, but I do not know what conclusion they reached. Weiser (1944), in Palestine, reported considerable success with breathing exercises in a small group of selected patients.

Helium Oxygen Inhalation.—Barach (1936) made a very novel and excellent contribution in the introduction of a helium-oxygen mixture in the treatment of patients in status asthmaticus and in those who, though perhaps not yet in extremis, have become so insensitive to the action of epinephrine as hardly to respond to the drug at all. His argument was that the dyspnea in these cases is not due to oxygen want, or to the presence of carbon dioxide in excessive quantity, but to the fact that in the presence of plugged bronchi, the muscles of respiration are exhausted to the point of impending cessation of activity in their effort to maintain the normal velocity of air movement demanded by the mechanism which reflexly controls the respiratory activities. His proposal of helium as a new therapeutic gas was based on the conception that its decreased specific gravity in relation to nitrogen (it is only one-seventh as heavy) would make a helium-oxygen mixture easier to breathe than a comparable nitrogen-oxygen mixture such as occurs in air. When put to the test the idea was soon proved to be correct, for patients were not only quickly brought out of their serious condition but they also regained in considerable measure their ability to obtain the usual relief from epinephrine. The mixture (helium, 80 per cent; oxygen, 20 per cent) has since been successfully used by many observers. Barach (1940) concluded that 90 per cent of his 84 patients with severe intractable asthma were decisively benefited by the regimen; in his most recent reports (1943–44) he ascribes even better results to the combined use of helium-oxygen and aminophylline by rectum.

Cooke (1943), objecting to the "prohibitive" cost of helium, finds oxygen introduced alone through the nasal catheter entirely satisfactory.

Special Diets.—Of course the whole gamut of dietary experiments has been run in this disease, but the most rational would seem to be the ketogenic regimen, as tried out by Peshkin and Fineman (for methods of inducing ketosis, see Index); Montagnini (1934) reported success in accomplishing the disappearance of crises and initiation of general improvement in all of his small series of cases. On the other hand, it is not difficult to see how dextrose

feeding may also succeed, since the liver, which functions best when well supplied with sugar, is known to play a large part in antigen-antibody reactions. Moll's (1932) success with liver diet, as used in pernicious anemia, is worthy of note.

Dextrose and Sodium Chloride Intravenously.—Wilson recommended the intravenous administration of dextrose solution in intractable cases, in 1935, since which time the measure has been much employed in recognition of the considerable likelihood of the patient to be severely dehydrated after two or three days in which he has been unable to swallow. Rackemann (1944) says that the administration of 1500 cc. of normal saline solution containing 5 per cent dextrose usually effects relief even when the patient is in extremely great distress; this, he points out, is quite in accord with the observation of Sheldon *et al.* (1939) that a marked loss of water and sodium occurs during an asthmatic attack.

Dehydration Therapy.—The exact reverse of the above is sometimes practiced by Cooke (1943), who says that perhaps dehydration effects relief by causing a shrinking of the bronchial wall. He places severely stricken patients on weak tea, fruit, or vegetable juices without salt, gives a couple of compound cathartic pills at night and ½ ounce (15 gm.) of magnesium sulfate in the morning, and follows this in three or four hours with an enema or preferably a colonic irrigation. He says that with enough sugar and sedation, and allowing water to be taken freely, this regimen may be maintained for three or four days, and may be followed by small, frequent, salt-poor feedings. Cooke says that he also sometimes succeeds temporarily through the use of 50 to 100 cc. of sucrose intravenously, a dehydrating measure earlier suggested by Keeney—may it not be significant that he adds "especially when 0.2 to 0.4 cc. of epinephrine is added"?

Fever Therapy.—All practitioners of wide experience know that a bout of fever often entirely relieves allergic maladies for the time being, and in some instances even for a long period following recovery from the intercurrent acute infectious process. Latterly a number of attempts have been made to accomplish the same thing by fever artificially induced as in the treatment of neurosyphilis, but the results so far have not shown this type of therapeutic approach to be as strikingly and consistently effective as one would desire from therapy as radical as this. Hyde's (1940) report is the latest I have seen.

Iodized Oil Insufflation.—The introduction of iodized oil into the tracheobronchial tree in the effort to force out bronchial plugs and purulent material had some vogue a few years ago but this therapy has been abandoned by conservative men because of its two dangerous features, namely, localized lipoid pneumonia and the chronic irritation and infection established about the point where the oil remains in the bronchial tree.

Niacin (Nicotinic Acid).—A number of men have been using this agent as an adjuvant when the other drugs are not proving very effective (Maisel and Somkin, 1942, Neuwahl, 1942, Melton, 1943). It is usually given intravenously in 50 to 100 mg. dosage two or three times daily, but in some instances seems also to work well when given orally.

Phenytoin Sodium (Dilantin).—Shulman (1942) has made a preliminary report of use of this drug with excellent results in 6 of 7 children with severe refractive asthma of the "extrinsic" type. It was given for periods of five to twelve months and all other medication stopped. Dosage was ½ grain (0.03 gm.) twice or thrice daily, though some patients required twice this dosage. Shul-

man noted some personality improvement and suggested that phenytoin might find its best usefulness when a strong psychogenic factor exists.

Sulfonamides.—These drugs have of course been tried. The instances in which the clearing up of a chronic infection with them has relieved the asthma are very few.

Bronchoscopy.—Bronchoscopy is occasionally used for the removal of sticky plugs from the bronchi. Friedberg (1943) reviewed the literature and described 8 of his own patients who were relieved by the measure, but 4 of these were children in whom the asthma cleared upon removal of a foreign body, 1 patient had a broncholith, 1 had a pulmonary abscess and 2 had stenosis of a bronchus which was due in one of them to tuberculosis.

Operative Procedures.—On the Continent, Gobell reported, in 1933, that he had been practicing double sympathectomy and vagus section for a number of years. In England, Levin (1935) preferred neurolysis by absolute alcohol injections and reported that complete relief was obtained in three fourths of the 23 cases which he treated this way. In New York, Stern (1937) also used this method. In Baltimore, Rienhoff and Gay (1938) employed bilateral resection of the posterior pulmonary plexus. Of course none of these surgical procedures is resorted to in any save the most intractable cases. One would think that certainly all other possible measures would have to be exhausted before resorting to such radical procedures. Cooke (1943) believes the removal of tonsils and adenoids, and sometimes sinus operations, of value in selected cases of intrinsic asthma, but Rackemann (1944) states his considered opinion that sinus surgery does not often effect a cure.

ANGIONEUROTIC EDEMA AND URTICARIA

Urticaria, or "hives," is characterized by the sudden appearance in the skin of a firm, elevated, whitish patch, which is surrounded by a pink zone and is accompanied by intense itching or stinging sensations. The lesion may be single or multiple and usually resembles in size the wheal caused by the ordinary mosquito bite; in the cases known as "giant" urticaria, however, the individual lesions are much larger than this and several often coalesce to form a relatively enormous patch, while in infants and young children urticaria frequently assumes a papular, vesicular, or bullous form. The wheals disappear in a few minutes to hours or, in the more severe cases, may persist for several days or even weeks. It is usual for hives to appear in crops with relatively long asymptomatic periods between, but some individuals are rarely free from these distressing lesions for more than a few days in succession. In angioneurotic edema the subcutaneous tissues as well as the skin participate in the transient swelling, which usually affects the forehead, eyelids, or lips, and is only rarely accompanied by pronounced subjective symptoms; when the internal organs are involved also, as is very occasionally the case, the symptoms may of course simulate almost anything. All the recorded fatalities have been due to sudden edema of the larynx.

THERAPY

It is unfortunately still the tendency of many physicians to approach these cases, especially the urticarial ones, largely from the dermatologic standpoint. This is decidedly wrong because the entities are certainly allergic manifesta-

tions and the only hope of alleviating the symptoms lies in making a thorough allergic study of each individual patient by the same methods which would be employed in hay fever or asthma. It is undeniably true that the result of such examinations will be negative in a very large proportion of cases, but nevertheless in the present state of our knowledge there is nothing else to do. Plenty of positive skin reactions will be found, but these usually only serve to demonstrate the antigens towards which the individual is sensitive in addition to the elusive one or more which are responsible for his hives. Still, many patients know from experience that certain foods will bring on an attack, and the approach to the problem in these patients through the elimination diets, as discussed in Food Allergy, will sometimes reveal one or more additional articles of diet that are causative. Other patients, who have not suspected a dietary factor themselves, are occasionally properly placed in this way also. Then there are the cases, an increasing number in the literature, due to physical or drug allergy. To repeat, the whole allergic gamut must be run, and the detection of an intrinsic or extrinsic etiologic factor will be the great though rare reward.

A few special things might possibly merit mention. Menagh found biliary tract drainage effective in relieving some cases; other types of focal infection have rather frequently been associated in the causative role with urticaria. Some patients are almost at once relieved by brisk saline catharsis, but they are certainly in the minority; perhaps it is only those whose symptoms are due to food allergy who obtain this relief. The administration of dilute hydrochloric acid as in achlorhydria, or just the opposite, alkaline therapy, is sometimes helpful; the latter is supplied by taking 20 to 30 grains of citric acid in a glass of water with each meal, or in the following simple prescription:

℞	Potassium citrate	℥j	30.0
	Syrup of orange	℥ ij	60.0
	Water to make	℥iv	120.0

Label: 1 teaspoonful after meals and upon retiring.

Of course the vitamins have had full play. Vaughan (1940) said that he had occasionally seen the intravenous administration of 30 grains (2 Gm.) of methenamine succeed when all factors of suggestion could be eliminated (one might slowly inject 5 cc. of a 40 per cent solution sterilized by boiling). Histamine, and also histaminase (see Asthma for methods), have been used successfully in a few instances, but Laymon and Cumming (1939) were unable to draw any conclusions regarding the efficacy of the latter agent in their small series of cases, and Toomey *et al.* (1944) found it worthless. The calcium salts are often used but there is little evidence of their efficacy, though recently Chambers and Bernton (1944) have been highly pleased with their results when they combined three times daily dosage of 5 grains (0.3 Gm.) of calcium lactate with 20 mg. of nicotinic acid twice daily with meals. Cornbleet (1935) said that the analgesic drugs act as "systemic antipruritics," a rather wishful terminology, it seems to me: phenyl salicylate, 5 grains (0.3 Gm.) in capsules, 2 of which are taken at meals and at bedtime; acetanilid, 3 grains (0.2 Gm.) every two to four hours as required. Epinephrine (see Asthma for methods) usually gives considerable relief during the attack. Kojis (1942) gave 10 units of insulin in 14 cases associated with serum sickness, with some benefit in 5; Stout and Kositchek (1940) gave dextrose intravenously with excellent results in 10 cases of the same sort.

For local application, nothing perhaps gives so great relief as "pink lotion" (see Index). Fantus recommended the application of any one of the following solutions, applied as hot as can be borne and followed, without drying, by dusting with talcum: sodium bicarbonate, 1 to 5 per cent; sodium carbonate, ½ to 3 per cent; borax, 1 to 4 per cent. According to Cornbleet an acid lotion is sometimes more effective: 1 part of vinegar to 2 parts of water or alcohol. Before resorting to the alkaline bath (1 teacupful of sodium bicarbonate to the tub), or the acid bath (1 or 2 cups of vinegar to the tub), or the colloid bath (see Index), all of which may be antipruritic, it is well to make sure that the patient is not of the type of physical allergic whose symptoms are aggravated by warming the body. Marchionini and Korth (1934), on the other hand, found sweat baths helpful in some of their cases.

FOOD ALLERGY

It is not possible in a single small volume of this nature to describe the host of ailments which investigators nowadays recognize as being in all probability allergic manifestations to specific food substances; chief among them, however, are many cases of the following: migraine, hay fever, asthma, eczema, several other dermatoses, gastro-intestinal disturbances which may simulate any of the well-known acute or chronic syndromes, some cases of urticaria and angioneurotic edema; and, one may add, many other ailments whose allergic nature is oftentimes not suspected until demonstrated through proved hypersensitivity to a food substance.

THERAPY

Roentgen Study.—Squier (1940) makes the point very positively that a gastro-intestinal examination by a competent roentgenologist, to rule out as nearly as possible organic disease, is an indispensable first step if one is dealing with suspected gastro-intestinal allergy. There does not seem to be anything very convincing in the recent studies of Wing and Smith (1942) and Fries and Mogil (1943) that roentgen observations are of much diagnostic aid with regard to the allergy itself.

Leukopenic Index.—Specific desensitization usually fails in these cases; indeed, skin reactions to the offending food are not always positive nor to be relied upon. A few years ago Vaughan offered a new means of detecting the food which causes the symptoms through the serial performance of white blood counts, the so-called "leukopenic index." The test as run today usually consists in having the patient report at 9:00 A.M. in a fasting state of at least twelve hours' duration. After thirty minutes' rest, two fasting counts are made at ten-minute intervals; then during about five minutes the patient eats an average portion of the food to be tested, and subsequent counts are made at fifteen- or twenty-minute intervals for one hour, the patient sitting quietly without talking or smoking during this time. The food is heated to body temperature but is eaten without condiments; except in intractable allergies the food is eaten for several days before the test. If any of the counts after eating falls more than 1000 below the mean of the two fasting counts the index is considered positive; if the fall is less than this but maintained throughout

the three counts it is considered "probably" positive. It is said that there may be delayed positives which will not appear within the arbitrary test period and that in case of doubt the period should be prolonged to two, three, or even four hours. The reliability of the leukopenic index has been questioned by the thorough studies of Loveless *et al.* (1938) and Brown and Wadsworth (1938), but upon the other hand, Hanson (1941), studying the method exhaustively upon himself, found it of diagnostic value. Obviously at best it is still in the experimental stage. Squier and Madison find that an eosinophil increase occurs as regularly as does a total leukocyte reduction, and they recommend simultaneous counting of eosinophils and leukocytes to increase the accuracy of the index. Of course the value of such a test as this, should its usefulness be generally confirmed, would lie in the fact that through it the offending food substance might possibly be more easily detected than through the employment of elimination diets.

Elimination Diets.—Rowe has exhaustively exploited the possibilities of this type of treatment. After eliminating at the beginning such foods as the patient definitely dislikes or knows to disagree with him, further study of the case is based upon the use of "elimination" diets (Table 11), consisting of foods which experience has shown rarely cause symptoms. Rowe says that Diets 1 and 2 may be prescribed separately or together, modifying them by substituting similar foods for any in the diets to which skin reactions or known idiosyncrasies exist. If sensitization to cereals as a group is suspected, Diet 3 may be used initially. Diet 4 may be used if the patient does not give any indications of milk sensitization, other foods being gradually added and the effect of each watched. On whatever diet is chosen, the patient should be encouraged to eat enough to prevent loss of weight, the physician substituting similar foods for any causing disturbance. If symptoms are relieved, one or two vegetables or fruits may be added the second week, and during succeeding weeks the other foods, always eliminating any which cause recurrence of symptoms; wheat, eggs and milk should be added last and their effect carefully scrutinized. Soybean milk (Sobee) is sometimes used as a substitute in patients sensitive to cow's milk; Cemac contains beef and vegetables.

With full cooperation, it is said that patients can usually be got up to satisfying and nutritionally correct diets in a few weeks, but sometimes the process requires months or even years. That it is often extremely difficult to maintain nutrition in patients sensitive to many things has been emphasized by Alvarez (1939), who states also that foreign foods not often eaten by native Americans can frequently be profitably employed. It is my feeling that sufficient stress has not been laid upon the possibility of vitamin deficiencies arising during the course of elimination dieting; these patients, it seems to me, should be given synthetic niacin (nicotinic acid), riboflavin, thiamine, and possibly ascorbic acid and carotene (see Index for methods). In the hands of Rowe the results are excellent in a wide variety of allergic disturbances, though the psychic effects of "dieting" must not be overlooked. This is a type of specific therapy which, because of its freedom from dangers, its relative simplicity and its inexpensiveness, deserves a wider trial than it has perhaps been given—if only patients were not so prone to snitch forbidden foods!

Food Diaries.—Many allergists find this the easiest and most efficacious method of determining the food or foods to which the patient has become sensitized. It consists merely of having the patient keep a complete record of every food or other injected substance taken over a long period of time, usually

a month or more, noting at the same time the appearance, disappearance, or aggravation of symptoms associated with the ingestion of food on a given day. Great simplification is of course obtained by having all mixtures such as stews omitted during the test period.

TABLE 11.—ELIMINATION DIETS FOR THE TREATMENT OF FOOD ALLERGY (ROWE)

Diet 1.	Diet 2.	Diet 3.	Diet 4.
Rice Tapioca	Corn Rye	Tapioca White and sweet potato	Milk*
Rice biscuit Rice bread	Corn pone Corn rye muffin Rye bread Rye crisp	Lima bean potato bread Soya bean lima bean bread	
Lettuce Spinach Carrot Beet Artichoke	Tomato Squash Asparagus Peas String beans	Beets Carrots Lima beans String beans Tomato	
Lamb	Chicken Bacon	Beef Bacon	
Lemon Grapefruit Pears	Pineapple Peaches Apricot Prunes	Lemon Grapefruit Peaches Apricot	
Cane sugar Wesson oil Olive oil Salt Gelatin Syrup made of maple sugar or cane sugar, or cane sugar flavored with mapleline or maple sugar Olives Pear butter	Cane sugar Mazola oil Wesson oil Salt Karo corn syrup Gelatin	Cane sugar Olive oil Wesson oil Gelatin Salt Olives Maple syrup or syrup made with cane sugar flavored with maple	

* Milk should be taken up to 2 or 3 quarts a day. Tapioca cooked with milk and milk sugar also may be taken.

Note: Wesson (cotton seed) oil is included in all diets. With allergy to cotton seed as shown by skin test or history this must be excluded and a cotton seed oil shortening such as crisco must not be used. If allergy to cane sugar is suspected, beet sugar or corn glucose may be used.

The Addition Diet.—In this regimen the patient is put on a basal ration usually of lamb, butter, rice, sugar and water, as suggested by Alvarez some years ago, and then foods are added one by one and their effect studied. Of course it is difficult to employ this method in persons who are very active.

Synthetic Diets.—Olmsted *et al.* (1944) have been experimenting with a synthetic diet comprising a mixture of amino acids, oil, dextrose, salt and

vitamins, but the methods are still far too cumbersome to merit present description.

Desensitization by Mouth.—*Peptone Method.*—Both the French and English schools had for some time been using peptones by mouth in cases of food allergy with indifferent results, when Luithlen, in 1926, showed that the fault probably lay in the use of preparations that were not truly specific. Urbach, who very actively carried on the investigations in Vienna and has continued

TABLE 12.—PROTEIN DILUTION METHOD OF DESENSITIZATION IN FOOD ALLERGY (KESTON, WATERS AND HOPKINS)

Directions.—Beat an egg so that yolk and white are well mixed; then add the prescribed amount of egg to ordinary water and mix well. Take 1 teaspoonful of the solution once a day unless otherwise directed. Throw away the rest of the solution. Make up a fresh solution every day. Use a dilution of the same strength every day for four days.

Mix ¼ teaspoonful	egg with 2	quarts of water.	Take ¼	teaspoonful.
Mix ¼ teaspoonful	egg with 3	pints of water.	Take ¼	teaspoonful.
Mix ¼ teaspoonful	egg with 2	quarts of water.	Take ½	teaspoonful.
Mix ¼ teaspoonful	egg with 3	pints of water.	Take ½	teaspoonful.
Mix ¼ teaspoonful	egg with 2	quarts of water.	Take 1	teaspoonful.
Mix ¼ teaspoonful	egg with 3	pints of water.		
Mix ½ teaspoonful	egg with 2	quarts of water.		
Mix ½ teaspoonful	egg with 3	pints of water.		
Mix 1 teaspoonful	egg with 2	quarts of water.		
Mix 1 teaspoonful	egg with 3	pints of water.		
Mix 1 teaspoonful	egg with 1	quart of water.		
Mix 2 teaspoonfuls	egg with 3	pints of water.		
Mix 1 teaspoonful	egg with 1	pint of water.		
Mix 2 teaspoonfuls	egg with 1½	pints of water.		
Mix 1 teaspoonful	egg with 1	cup of water.		
Mix 2 teaspoonfuls	egg with 1½	cups of water.		
Mix 1 teaspoonful	egg with ½	cup of water.		
Mix 2 teaspoonfuls	egg with ¾	cup of water.		
Mix 1 teaspoonful	egg with ¼	cup of water.		
Mix 1 teaspoonful	egg with 3	tablespoonfuls of water.		
Mix 1 teaspoonful	egg with 2	tablespoonfuls of water.		
Mix 2 teaspoonfuls	egg with 3	tablespoonfuls of water.		
Mix 1 teaspoonful	egg with 1	tablespoonful of water.		
Mix 4 teaspoonfuls	egg with 3	tablespoonfuls of water.		
Mix 2 teaspoonfuls	egg with 1	tablespoonful of water.		
Take 1 teaspoonful of raw egg.				
Take 1½ teaspoonfuls of raw egg.				
Take 2 teaspoonfuls of cooked egg.				
Take 3 teaspoonfuls of cooked egg.				
Take 4 teaspoonfuls of cooked egg.				
Take ½ cooked egg.				
Take ¾ cooked egg.				
Take a whole egg.				
After this eat at least 1 egg every few days.				

them since coming to this country, demonstrated that the treatment is worthless unless the exact peptone toward which the patient is sensitive is employed; for example, if an individual cannot eat chicken, the peptone to be used must be made from the flesh of the chicken, and if eggs are the offender, the peptone must come from the white of eggs. Small doses of these specific peptones (Urbach [1943], calls them propeptans) are then given by mouth before each meal in which the offending foods are to be included (these foods having been determined by an elimination diet regime much like Rowe's, see above), in the

belief that not only can the individual attack be thus prevented but that desensitization will also take place in time. The ingestion of the peptone must occur exactly three-quarters to one hour before the meal and a considerable time after digestion of the last meal has ceased; it is therefore necessary to forbid all between-meals eating, which means of course that cooperation is difficult to obtain in children and that the method is hardly practicable in frequently fed infants.

This type of desensitization has not caught on at all in the United States.

Protein Dilution Method.—This, the American variant of the above method, as devised by Keston, Waters and Hopkins (1935), I am presenting here because its simplicity and inexpensiveness seem to warrant its being given a trial by general practitioners. The proposers of the method, and more recently Edwards (1940), have reported its successful employment in small series of cases and there are numerous physicians with single case successes; specialists in allergic diseases are notably reticent in the matter. The method consists in attempting to desensitize patients, in whom sensitization has been proved by elimination diets or other tests, through feeding by mouth gradually increased amounts of the convicted protein in the natural form in which it occurs in the offending foods. The chart (Table 12) indicates the procedure in instances of sensitization to egg only; Keston *et al.* offer slight variations in dilutions in connection with the other foodstuffs they have successfully used, but since they found greater difficulty in desensitizing patients allergic to egg than those sensitive to other substances, I imagine the substitution of any other food in equal quantity for the amounts of egg shown in the chart would err only on the side of conservatism. It must be understood by one who would try this method that during its use the patient must absolutely take no foods in which even the minutest amount of the offending substance could possibly be present; to insure such complete absence of the substance from the diet is in itself a matter of no little difficulty.

Pancreatic Enzyme Method.—Oelgoetz *et al.* (1935) believed that food allergy may be caused by a decrease in the concentration of serum enzymes with the result that whole proteins reach the body cells, where they may exert an irritant action. They attempt to compensate for this alleged deficiency by giving the patient by mouth a 50 per cent glycerin extract of the whole fresh pancreas, giving an amount after each meal equivalent to 5 grains (0.3 Gm.) of an active dry powder. Bradley and Belfer (1939) find much that is unsound in the theoretical basis of this work, but they do not deny that a slow cleavage of protein in the digestive tract may increase the chances of absorption of antigenic molecules into the blood stream. And so the matter stands at present.

SERUM DISEASE

Serum disease is an allergic reaction caused by the parenteral introduction, by whatever route, of foreign serum. The usual symptoms are a mixture of urticaria and erythema, fever, arthritis without pronounced objective changes in the joints, swollen and tender lymph nodes, and edema of various portions of the body accompanied by urinary evidences of temporarily impaired renal function. In some instances reactions in the internal organs may give rise to

symptoms which will be very confusing if the fact of serum disease is not kept in mind. In a very small proportion of cases (Bennett, 1939), usually following the introduction of tetanus antitoxin, severe neuritis occurs. The time elapsing between the giving of the serum and the appearance of the disease is usually seven to twelve days; in most cases the symptoms disappear in four to six days, but occasionally they persist for as long as two weeks. Recovery is the rule, though relapses are not uncommon. Kojis' (1942) exhaustive review of this subject is commended to the reader.

THERAPY

Serum sickness cannot be prevented nor can it be very satisfactorily treated by any routine methods devised to date. For methods of relieving the itching, see Angioneurotic Edema and Urticaria. The arthritis does not respond to salicylates. Calcium salts have been advocated on and off through the years, but it is certainly not the consensus that they are worth the giving. Histaminase (see Hay Fever for method) has been employed with apparently considerable resultant relief by Foshay and Hagebusch (1939), and Cherry and Prickman (1941), but the latter authors recognize that much more experience must be had before the true worth of the agent can be known, since in some of their cases the relief ascribed to the influence of histaminase might only have been spontaneous.

PHYSICAL ALLERGY

The demonstrations of Duke, confirmed by others, have impressed the profession with the fact that any of the bizarre manifestations commonly laid at the door of neurasthenia, psychasthenia, vagotonia and so on, as well as the more orthodox allergic syndromes, may not infrequently be due to heat, effort, cold, or light sensitiveness.

THERAPY

Persons highly sensitive to heat from without should avoid exposure to high temperatures as much as possible, of course, and will do well to move into a cool, dry climate. Since they are nearly always susceptible to attacks as the result of internal liberation of heat also, avoidance of physical activity is a part of the treatment as well. Temporary relief can nearly always be obtained by the taking of a cold bath. Cold-sensitive individuals can usually protect themselves fairly well by the use of adequate clothing and by taking care never to expose themselves to low temperatures when they cannot rather vigorously exercise at the same time. For such persons swimming, whether in an artificial pool or natural body of water, is always particularly dangerous; many individuals have doubtless drowned through unrecognized hypersensitivity of this sort. A hot bath is probably the quickest and simplest way in which to counteract the effects of chilling in cold-sensitive individuals. When the patient is severely enough afflicted that the mere exposure of a small portion of the body surface, such as placing the hands in tapwater, will bring on symptoms, the occupational phase of the malady may assume considerable importance. Duke reported that he was able to desensitize some individuals by accustoming them to plunge into a cold bath for a few seconds every morning; in others he employed a rapid ice rub all over the body. In other instances he prevented an

early morning attack by warming up the patient thoroughly by a hot bath at midnight. Horton *et al.* (1936), at the Mayo Clinic, stated that the average cold-sensitive patient can be adequately desensitized by having him immerse a hand in water at 50° F. for one to two minutes twice a day for three to four weeks; in some instances they have also succeeded by starting with the water at 65° F. and decreasing the temperature to 45° F. for increasing periods. Some of their patients have likewise been desensitized by subcutaneous injection of 0.1 mg. of histamine twice daily for two to three weeks.

Histaminase (methods in Hay Fever) has been successfully used in a small number of cases by Roth and Horton (1937), Vaisberg (1939) and Baker (1940); but Peters and Horton (1941) have also reported a failure.

In light sensitiveness the problem is much more difficult of solution because adequate protection from exposure is practically impossible. Many years ago attention was called to the fact that injection of hematoporphyrin into experimental animals rendered them light-sensitive, and practical deduction from the observation was made in pointing out that buckwheat contains phyloporphyrin, a similar substance. Since this substance may also occur in ordinary wheat and in oatmeal, it would seem advisable to investigate the effect of cereal-free diets on light-sensitive patients, even though the studies of Templeton and Lunsford (1932) cast some doubt on the significance of the porphyrins in this connection. The ingestion of quinine, acriflavine and other fluorescent substances, as well as the taking of sulfonal, or the presence of lead poisoning or liver insufficiency, have all been associated with some cases. To diminish the penetration of ultraviolet rays, it has been stated (J.A.M.A., 102, 1103, 1934) that 5 per cent of disodium naphthol sulfonate in solution in alcohol or in an ointment base may be effective.

DRUG ALLERGY

In recent years evidence has been accumulating that sensitization to ordinary as well as to some extraordinary drugs is a much more common occurrence than had been previously suspected. I cannot gather together here, merely to list them, the large number of drugs already implicated, but the reader will find the chief among them discussed from this standpoint at those places in the book where such consideration seems most appropriate, for example: organic arsenicals in syphilis, cinchophens and acetylsalicylic acid (aspirin) in rheumatic affections, amidopyrine in agranulocytosis, the sulfonamides in the chapter on the toxicities of this group, etc. Quick (1934) has proposed that drugs which produce allergic reactions such as urticaria, angioneurotic edema and vasomotor disturbance may perhaps also cause a severe inflammatory reaction terminating in necrosis comparable to the Arthus phenomenon familiar to experimental workers. The acute yellow atrophy of the liver caused in susceptible individuals by cinchophen, and the granulocytopenia sometimes appearing allergically upon the ingestion of amidopyrine, he would explain upon this basis. The important practical point in connection with this suggestion is that any patient experiencing urticaria that is at all related to the taking of a drug should never again be given another dose of that drug if one would not court the more serious reactions.

DEFICIENCY DISEASES

SUBCLASSICAL DEFICIENCY STATES

The majority of the world's population has not and never has had enough to eat in terms of dietary adequacy. Poverty, faulty food distribution and bad dietary habits are the chief underlying causes of this wretched state of affairs. The classical deficiency diseases dealt with in this chapter are easy enough to recognize and usually to treat, but leaders in this field of study have pointed out two facts: (*a*) that deficiency in a single nutritional factor is rare, *i.e.*, most of the syndromes as seen by the practitioner are multiple and not single deficiencies; and (*b*) that the classical deficiency diseases all have their subclassical phases. It does not simplify matters either that in the current state of our knowledge the diagnosis of a subclassical deficiency must be made in practically all instances without the aid of either methods or instruments of precision, though the study of Ruffin *et al.* (1944) indicated that perhaps in time lab-

TABLE 12a.—A PROBABLY ADEQUATE DIET

Milk. Two or more glasses daily for adults; 3 or 4 or more glasses daily for children. This may be drunk as such or combined with other foods.

Vegetables. Two or more servings daily in addition to potatoes. Preference should be given to the green leafy and the yellow vegetables because of their vitamin A. One vegetable might well be eaten raw if it is a good source of vitamin C.

Fruits. A serving or more of fruits is desirable but preference should be given to fruits which contribute vitamin C. Citrus fruit and tomatoes (some will consider this a vegetable) are outstanding sources, and the commercially canned products are as good as the fresh.

Meats and other protein foods. There should be one serving of meat for its protein content. Additional servings will supply more protein and more thiamine, riboflavin and nicotinic acid which meats provide. Fish, cheese and legumes also provide proteins but as a rule are poorer in the B vitamins. Eggs are valuable protein foods and also supply some iron and riboflavin and vitamin A.

Cereals and bread, and butter and other fats. These are the energy foods. In selecting them it is well to choose those items which contribute additional food values. Thus the cereal products ought to be whole grain or enriched. Fats ought to be butter which contains vitamin A. If oleomargarine is used for economy, then it would be well to select that which supplies added vitamin A.

(Bing, 1943.)

oratory determinations of vitamin levels may become very useful in these situations. In our own country most of the gross deficiency exists in the South, but Jolliffe, McLester and Sherman (1942), studying the dietary inadequacies and malnutrition throughout the country, as an assignment from the National Research Council, give it as their considered opinion that the nutritional status of an appreciable part of the American population can be distinctly improved. Of course the correction of the dietary inadequacies of whole populations is a task that does not lie within the province of the practicing physician, though it is certain that if physicians everywhere could be deeply stirred by the tragic lack of necessity for the amount of malnutrition which obtains in the world today, the task of those governmental agencies, public health authorities and other properly constituted bodies whose lot it is to attempt

alleviation of the situation would be tremendously lightened. It is, however, very much the physician's job to recognize and treat deficiency states in individuals who are his patients. Of course as also in other types of disease, the thing which most facilitates diagnosis is to suspect the presence of the entity.

Spies (1944) says he suspects nutritional deficiencies in the following groups: (1) Those who for any reason have a food intake below that recommended

TABLE 13.—CONDITIONING FACTORS THAT MAY CONTRIBUTE TO NUTRITIONAL FAILURE

I. *By Interfering with Food Intake*
1. Gastro-intestinal diseases as:
   - Acute gastro-enteritis
   - Cholecystitis and cholelithiasis
   - Peptic ulcer
   - Diarrheal diseases
   - Carcinoma of stomach and esophagus
2. Food allergy
3. Mental disorders as:
   - Neurasthenia
   - Neurosis
   - Psychoneurosis
   - Psychosis
4. Operations and anesthesia
5. Infectious diseases associated with anorexia
6. Loss of teeth
7. Heart failure (anorexia, nausea, and vomiting by visceral congestion)
8. Pulmonary disease (anorexia, vomiting due to cough)
9. Toxemia of pregnancy (nausea and vomiting)
10. Visceral pain (as in renal colic, and angina that reflexly produces nausea and vomiting)
11. Neurologic disorders which interfere with self-feeding
12. Migraine

II. *By Interfering with Absorption*
1. Diarrheal diseases as:
   - Ulcerative and mucous colitis
   - Intestinal parasites
   - Intestinal tuberculosis
   - Sprue
2. Gastro-intestinal fistulas
3. Diseases of liver and gallbladder
4. Achlorhydria
5. Carcinoma of the stomach

III. *By Interfering with Utilization*
1. Liver disease
2. Diabetes mellitus
3. Chronic alcoholism

IV. *By Increasing Requirement*
1. Abnormal activity, as associated with prolonged strenuous physical exertion with lack of sufficient sleep or rest, delirium and manic-depressive psychoses
2. Fever
3. Hyperthyroidism
4. Pregnancy and lactation

V. *By Increasing Excretion*
1. Biliary or gastro-intestinal fistula
2. Perspiration
3. Loss of protein in nephritis and nephrosis
4. Polyuria, as in:
   - Diabetes mellitus
   - Diabetes insipidus
   - Long-continued excessive fluid intake as in urinary tract infections
5. Lactation

VI. *By Therapeutic Measures*
1. Therapeutic diets, as in:
   - Sippy regimen
   - Gallbladder disease
   - Anti-obesity diets
2. Antacids
3. Mineral oil
4. Infusions
5. Diuretics
6. Fever therapy
7. Paracentesis and thoracentesis

(Jolliffe and Smith, 1943.)

for an adequate diet. (Bing, of the Food and Nutrition Board of the National Research Council, in 1943 published the dietary pattern presented in Table 12a as probably "adequate.") He points out that information in regard to income and food resources is often of value in determining the adequacy of the individual diet. If the amount of money available for food is small and if the patient has no food resources such as a garden, cow, or chickens, it is almost certain that his diet has been inadequate. He says that he and his associates

have found that many families have a good dietary immediately after payday but that it gradually tends to become poorer as the money diminishes; insurance payments, illness and other factors which make demands on the income often seriously affect the quality of the dietary. Emotional factors likewise tend to affect the food intake, especially in women who worry over their children and household problems or are working outside their homes and attempting to take care of their family and housework as well. Such individuals will often fail to eat a proper diet even when it is available. In such instances, though only one individual may present as the patient, deficiency diseases of either a classical or subclassical degree are likely to be found in all the members of the family.

(2) Persons who are chronically addicted to alcohol.

(3) Persons who have an organic disease which might interfere with the absorption or utilization of food or might increase food requirements. One might add also, as do Jolliffe and Smith (1943), see Table 13, conditions in which nutrients are lost by increased excretion or through the employment of certain therapeutic measures.

(4) Persons whose physical exercise is increased but whose diet is of borderline adequacy.

As a deficiency disease develops there occur functional disturbances arising from every part of the body and giving a complex clinical picture with a great variety of symptoms which may exist for months or years before characteristic lesions appear. Spies says that their group is particularly concerned with the following symptoms as suggesting the possible development of a deficiency state: loss of weight and strength; headaches; dizziness; burning sensations of the skin on various parts of the body; roughness and dryness of the skin; burning of the eyes, blurring of vision, lacrimation, photophobia and night blindness; burning and cramping of the stomach; burning of the tongue and lips; redness, swelling and ulcerations of the tongue and mucous membranes of the mouth; increased salivation; diarrhea; burning and cramping of the feet and legs. Central nervous system disturbances including insomnia, general nervousness, loss of memory, apprehension and hypersensitive emotional reactions are common symptoms which may appear early in the development of a deficiency state. These symptoms tend to come and go and with each recurrence become more severe until definite clinical evidence of one or more deficiencies appears.

THERAPY

Once the diagnosis has been made the conditions which have brought about the deficiency should be overcome if possible. Symptomatic treatment and the treatment of coexisting diseases should be undertaken. The patient should be put on a well-balanced diet of 3000 to 4000 calories with liberal amounts of minerals and vitamins and a daily supply of 120 to 150 Gm. of protein. Then therapeutic substances in sufficient amounts to correct the deficiency should be administered.

Spies and his group, in the great nutrition clinic at the Hillman Hospital in Birmingham, Alabama, in treating thiamine, niacin (nicotinic acid), riboflavin and ascorbic acid deficiency, give daily a basic formula containing 10 mg. of thiamine, 50 mg. of niacin, 5 mg. of riboflavin and 75 mg. of ascorbic acid. In the presence of a predominating deficiency they add more of the vitamins specific for that deficiency. In the case of thiamine deficiency 10 mg.

of thiamine are added daily; in riboflavin deficiency 5 mg. of riboflavin twice daily; in scurvy 100 mg. of ascorbic acid three times a day; and in mild pellagra 50 mg. of niacin amide three times a day. If the pellagra is severe, the patient is given 150 mg. of niacin amide three times daily in addition to the basic formula. When a patient is moribund from nutritive failure or there is interference with the absorption of nutrients from the intestinal tract, it may be necessary to administer the vitamins parenterally. When large amounts of dextrose are being injected intravenously daily, Spies recommends the inclusion of 20 mg. of niacin amide, 5 mg. of thiamine and 7.5 mg. of riboflavin, and in some instances he has found it desirable to inject 50 mg. of ascorbic acid in a sterile isotonic solution of sodium chloride. Dried brewers' yeast powder and liver extract are excellent therapeutic agents for the treatment of diseases arising from a B complex deficiency, being natural sources of niacin amide, thiamine, riboflavin, pantothenic acid, cholin, biotin, amino acids, enzymes, minerals and probably many as yet unknown nutritional factors. Spies uses from 2 to 6 ounces of yeast or liver extract administered orally; the latter of course can be injected also parenterally.

RICKETS

(Including Osteomalacia and Renal Rickets)

Rickets is a disease of infants which is characterized by a diminution in the inorganic phosphorus of the blood—or, in those cases in which there is an associated tetany, low calcium but approximately normal phosphorus—and a faulty calcification of the newly laid down bone tissue. It is encountered most frequently between the ages of six and eighteen months, its victims being for the most part well-nourished and rapidly growing children. The seasonal fluctuation of the disease is one of its most characteristic features, the case incidence rising from October to a peak in March and then falling to June; new cases very rarely develop in the summer. Rickets is most prevalent in the industrial cities of the north temperate zone and is infrequent in the tropics; indeed, in subtropical regions its occurrence is unusual except in the poverty-stricken class, in whom dietary deficiencies and bad hygienic habits permit the disease to exist despite the presence of plenty of winter sunshine A typical case of rickets shows the following symptoms: restlessness, especially turning of the head from side to side; irritability; sweating of the head; enlargement of the costochondral junctions, giving the rachitic "rosary," and enlargement of the epiphyses at the wrist; an abnormally open fontanel, coupled with a tendency for areas of softening to develop below the occipitoparietal suture. Squareness of the head, deformities of the chest (pigeon-breast or funnel thorax), knock knees or bowlegs, and curvature of the spine; any or all of these may be present. There is often "pot-belly" and usually some muscular weakness; the blood is deficient in inorganic phosphorus, which may fall below 3.5 mg. per 100 cc., and a radiograph of the lower end of the ulna shows certain abnormalities which are diagnostic.

Artificially fed infants are more prone to develop rickets than are the breast fed, though the latter are by no means infrequently attacked; prematurely born infants almost invariably become rachitic. It is felt by many pediatricians that the number of demonstrable cases of rickets, *i.e.*, those showing some of

the symptoms listed above, is not an accurate index of the prevalence of the disease, for it would seem possible, by careful examination, to elicit one or more signs of its presence in practically all rapidly growing infants; indeed, Eliot has even suggested that this state of affairs might be physiologic. It is felt at present that rickets is caused by deficiency in vitamin D (with associated calcium-phosphorus imbalance), in some other factor not yet determined, and by insufficient exposure to sunlight during the dark months. The prognosis in rickets *per se* is very good; even very pronounced deformities sometimes disappear when the period of most rapid growth is passed and sunny "open" weather comes round again. Tetany is the most frequent and pneumonia the most serious immediate complication. The most serious residual defect is deformed pelvis in the female.

Osteomalacia, which occurs almost exclusively in women in the child-bearing age, is generally conceded to be rickets in adults who are brought to the verge of calcium starvation by pregnancy, lactation, perhaps menstruation, and possibly also in some cases (Meulengracht, 1939) through disease of the digestive tract or the abuse of cathartics. The disease is not encountered in the United States but is prevalent in northern India, northern China and Japan; it occurs sporadically on the Continent, and an occasional case is seen in the British Isles. After War I "hunger osteomalacia" appeared among the peoples of Central Europe and we shall likely see it again after the close of War II. The therapy of osteomalacia requires no separate consideration from that of rickets.

In the most usual of several variants of the rare childhood entity known as "renal rickets" there are roentgenographic and perhaps gross (genu valgum) evidences of rachitic changes in the bony structures, but the outstanding features of the malady are dwarfism, persistent renal insufficiency due to chronic nephritis, double hydronephrosis, or congenital cystic kidney, sexual infantilism if puberty is reached, hyperphosphatemia, and death from azotemia.

Some historians think that at one place in the second Iliad of Homer (*circa* 950 B.C.) there is a clear description of rickets. In a number of the medieval holy pictures the Christ child is shown as strikingly rachitic. But the classic description of the disease was that of Francis Glisson, in 1650; indeed, so far as I know, this was the first account to appear in medical literature. In 1908, Finlay produced the disease experimentally for the first time by the use of a deficient diet.

PREVENTION AND TREATMENT

Cod Liver Oil.—Clinicians have used the oil empirically for a long time with excellent results in both the cure and prevention of rickets—unless we wish to apply the most delicate clinical tests to these results, in doing which it will be found to be very doubtful if any of the antirachitic agents is able absolutely to prevent the disease. In addition to readily digestible and assimilable fats, the oil contains vitamin D, which exerts a favorable influence on calcium and phosphorus metabolism and particularly in the prevention of rickets, and vitamin A. The antirachitic properties of the oil reside solely in the vitamin D and are not raised by ultraviolet irradiation. The administration of the oil to mothers very much lessens the incidence of rickets in breast-fed infants.

The standard of potency per gram of cod liver oil in the U.S.P. XII is not less than 850 of the new vitamin A units and not less than 85 of the new vitamin D units, these units being practically identical with "International Units,"

and the recommended U.S.P. dose of such an oil for infants is 2 teaspoonfuls (8 cc.) daily. As a matter of fact, most Council-accepted (1944) oils exceed in content the vitamin D standard—the important item in rickets—and therefore in selected cases their dosage can probably be somewhat lowered with safety. The usual procedure nowadays is to begin the administration with ½ teaspoonful of the oil when growth begins to accelerate—within two weeks of birth or at least before the end of the first month—and to increase dosage rapidly so that within a week 1 teaspoonful is being taken and in two weeks more the full dose of 2 teaspoonfuls is reached; this full dose is to be continued at least up to two years of age. Average dosage is usually somewhat augmented in the case of premature infants and in unusually rapid-growing infants; in Negro and Italian infants, with their marked predisposition to rickets, double doses should be reached if well tolerated, otherwise the oil should be fortified with viosterol. The only disadvantage of cod liver oil is its objectionable taste and odor. It is considered advisable to continue administering it through the summer even though there is adequate exposure to the sun, because once stopped it may be impossible to get it accepted again.

Rancid oil is a poor source of vitamin A, it is disagreeable in taste (*more* disagreeable, that is!), and it may account for some of the digestive disturbances in infants. Whipple's precautions for the prevention of rancidity: (*a*) Obtain a product in good condition. (*b*) Keep in refrigerator after opening. (*c*) Keep mouth of bottle free from dried residue. (*d*) Obtain only a six weeks' supply at one time.

The flavoring of cod liver oil, as is attempted in some of the Council-accepted brands, does not disturb its activity. Any of the Council-accepted preparations put up with malt extract may also be used satisfactorily.

Cod Liver Oil Concentrate.—There are several of these preparations which are Council-accepted (1944) as equivalent to cod liver oil. They are marketed as oils, or in capsules or tablets. Dosage varies with the amount of concentration and is therefore that which is stated on the package.

Substitute Fish Oils.—The advantage claimed for burbot, halibut and percomorph liver oils is that while fishy in taste they do not have the rancid taste and odor of cod liver oil. The dosage here stated is that of N.N.R. (1944) *Burbot Liver Oil:* 40 drops daily, or as prescribed. *Halibut Liver Oil:* for infants, 6 to 10 drops; premature and rapidly growing infants, 15 drops; severe deficiencies, 20 drops or more. *Percomorph Liver Oil:* normal infants, 10 drops daily; curative and in severe conditions to 20 drops daily. There is also available a *Shark Liver Oil*, the dose of which is one capsule, or about 8 minims, daily. The oils are available in soft capsules.

Viosterol in Oil.—Irradiated ergosterol is the most potent of the antirachitic agents in vitamin D content (U.S.P. XII requires 10,000 units of vitamin D per gram), but it does not contain the growth-promoting vitamin A. This preparation is tasteless; it may be dropped directly into the mouth or be floated on orange or tomato juice; incorporation with a feeding is considered bad practice as some of the oil may be lost on the sides of the bottle. Calciferol (vitamin D_2) in propylene glycol is soluble in water and hence can be mixed with the milk feeding without loss; drisdol, the N.N.R. (1944) accepted preparation, has an average daily dose of two drops if dissolved in the formula or four drops if administered in water or gruel, and up to sixteen drops daily for the premature or rapidly growing infant. Accepted dosage of viosterol in oil is: average infants, 5 drops daily (standard dropper in package); premature

and rapid-growing infant, 15 drops; daily curative dose, 15 to 20 drops; severe cases and adults, more than 20 drops. Among the more recent studies of dosage, that of Shelling and Hopper (1936) at the Johns Hopkins Hospital is typical of all the others in fully confirming the N.N.R. dosage for full term and premature infants and is especially worth citing because it was carried out on a very large number of patients. In 134 cases of active rickets they found that dosage was intimately related to the severity of the rickets; the mild group receiving 10 drops daily healed in five months; the group receiving 15 drops, in 4.3 months; the group receiving 20 drops, in 3.1 months. In the group receiving 30 to 60 drops healing time was not shorter, but these larger doses were given in late or very severe rickets in which smaller doses would have accomplished much slower healing. In their whole six years' experience evidence of viosterol toxicity was never encountered.

The fear, earlier entertained, of inducing a state of toxic hypercalcemia by use of doses much larger than the above, was probably unfounded since there are available many records of such high dosage administration without untoward effects. Tumulty and Howard (1942), to be sure, reported two cases in which the administration of repeated large doses of viosterol was associated with a prolonged hypercalcemia and persistent impairment of renal function, but it would seem that these cases may possibly be discounted since the patients were both young vigorous men immobilized in casts, a state of affairs which it is recognized in itself may produce hypercalcemia with resultant renal damage in young active individuals. Vollmer (1940) reported the successful use of single massive doses of viosterol in oil and ether, given intramuscularly, his injection mixture containing 600,000 units of vitamin D, 0.6 cc. of peanut oil and 0.4 cc. of ether. Krestin (1945) reported the successful prevention of rickets in 90 of 93 infants under two years who were given a single dose of 300,000 units of vitamin D_2 and then observed for a six-month period, the agent being given in the form of 7.5 mg. of calciferol dissolved in 1 cc. of oil and administered from a spoon after a milk feeding. Rambar *et al.* (1943) reported that the single massive oral dose of an electrically activated vaporized ergosterol (ertron), containing 600,000 U.S.P. units of vitamin D, was effective in preventing rickets in a group of infants studied during the fall and winter months. The use of repeated smaller doses of 100,000 U.S.P. units of the same agent given monthly from October to April was also effective in preventing rickets in all of the infants studied. Wolf (1944), using the same preparation, has been giving 50,000 units at one month of age, 50,000 units at two months, and 600,000 units at three months, administering the 50,000 unit doses in liquid form in the formula and the 600,000 unit dose in powder form in cereal. Two of his 21 infants showed slight roentgenographic rachitic changes one month after the second dose of 50,000 units, but after the 600,000 units were administered the processes were found to be healed four months and five days later; the remaining 19 infants showed no rachitic changes during the total observation period of from four to nine months.

Cod Liver Oil with Viosterol.—In this preparation we have oil fortified with viosterol to obtain four and one-half times as much vitamin D effect as can be obtained from the oil alone in usually tolerated doses. N.N.R. (1944) dosage: infants and young children, 2.5 to 3.3 cc. daily; adults and in severe cases, up to 7 cc. or more—this ridiculous fractional cc. dosage may be translated for practical men into approximately $\frac{1}{2}$ to 1 teaspoonful daily or 2 teaspoonfuls or more in severe cases.

Halibut Liver Oil with Viosterol.—This preparation is said to be less disagreeable than cod liver oil with viosterol and the same vitamin D effect may be obtained with smaller dosage. N.N.R (1944) dosage (standard dropper in package): infants, 8 to 10 drops daily; premature and rapidly growing infants, 15 drops; older children, 15 to 20 drops; adults, 20 drops or more. Available also in soft capsules.

Antirachitic Milk.—The Committee on Foods of the American Medical Association has had before it for some years the perplexing problem of the vitamin D fortification of milk for use in the prevention of rickets. A few years ago, however, Dr. Philip C. Jeans, of Iowa City, undertook a study of the subject for the guidance of the Committee, and as his excellent review, published in 1936, is still the most authoritative available I shall here set down what I make out to be his conclusions on the various types of product dealt with, merely adding in passing that Park (1940), of Johns Hopkins Hospital, feels that if there is doubt of these milks being an adequate source of supply in individual cases, they should be supplemented by one of the vitamin D preparations in oil—and he seems to consider it practically always wise to make this supplementation during the first year in the case of the irradiated milk and during the first six months for the fortified and metabolized milk.

Fresh Milk Containing Cod Liver Oil Concentrate.—When such milk contains 400 new U.S.P. units to the quart, and is fed in customary amounts to full-term infants, it will prevent rickets.

Evaporated Milk Containing Cod Liver Oil Concentrate.—Such milk, containing 135 new U.S.P. units to the quart, prevents rickets but it may permit a suboptimal intake of vitamin D as judged by calcium retention. If it contains 400 units it seems entirely adequate.

Irradiated Milk.—The results with irradiated evaporated milk agree with those of irradiated fresh milk. Such milk will prevent rickets in most full-term babies, but the vitamin D content approaches closely the minimum preventive level and permits what is believed to be suboptimal retention of calcium.

Metabolized (Yeast) Milk.—At the time of Jeans' review only one preventive study was available in which milk from cows fed irradiated yeast had been used, but several studies have now appeared and such milk has been standardized at 430 units per quart.

Phosphorus.—The administration of phosphorus has no legitimate place in either the prophylaxis or therapy of rickets, since the fault lies almost certainly in a failure of the calcifying mechanism rather than in faulty absorption of the bone salts.

Light Therapy.—Rickets may be both prevented and cured when infants are exposed in the light of a good type of ultraviolet-ray producing apparatus when properly used, these rays like those of natural sunlight converting the provitamin in the skin, 7-dehydrocholesterol, into vitamin D which is then absorbed into the blood stream. It would be out of place to attempt a description of the use of such apparatus here. It is the general belief in the profession that in the temperate zone in the summer, sunlight can be relied upon to prevent rickets provided the child is exposed outdoors, but the study of Moore *et al.* (1937) on nearly a thousand children showed that the percentage of rickets was nearly as high among the children of sunny San Diego, California, as among those of cloudy Portland, Oregon; they therefore concluded that under modern living conditions abundant sunshine does not protect and that therefore the use of an antirachitic is advisable. Park (1940) feels that under

special conditions summer sunshine may cure rickets but he thinks it should not be solely relied upon to do so. Winter sunshine is best regarded everywhere as practically nonantirachitic.

Treatment of Refractory Rickets.—These cases are usually encountered in children beyond infancy. There is nothing to do but push on to enormous vitamin D dosage. Bakwin *et al.* (1940) report the case of a boy who developed rickets at the age of six years, in which it was necessary to use 1,000,000 units daily for cure and 440,000 units daily for maintenance. Shohl and Butler (1939) found a mixture of citric acid and sodium citrate—two parts molar acid to one part molar salt—apparently in itself antirachitic; they added 50 cc. of the combined solutions to the formula as a diluent. Boyd and Stearns (1942) reported a case of chronic acidosis associated with severe rickets in which they felt that the administration of ½ teaspoonful of sodium bicarbonate three times daily during three years, the patient being eleven and one-half years old when first seen, increased the effectiveness of the vitamin D which was given the patient. A number of observers have felt that a secondary hyperplasia of the parathyroid gland occurs in rickets. Brakeley (1943) felt that her patient began to improve gradually after the irradiation of her parathyroids—a thing difficult to understand since most observers have felt that roentgen therapy is of no avail in hyperparathyroidism.

SCURVY

Scurvy is a disease which is caused by deficiency of fresh vegetables and fresh fruits in the diet. In infants it is most frequent between the fifth and fifteenth months of life, being quite rare after the twentieth month. In adults it occurs invariably whenever there is deprivation for as much as six months of foods containing vitamin C, now identified as ascorbic (cevitamic) acid. The symptoms in adults are: loss of vigor; a sallow complexion; pains, in the legs principally; shortness of breath; sore, bleeding, spongy gums; foul breath; and ecchymotic spots on the skin, especially of the legs. At the present time diagnosis usually is made before the condition has progressed very far, but when correction of the dietary deficiency is impossible, the patient rapidly becomes a pitiable object; the body becomes edematous, dyspnea and pain are quite agonal, intramuscular and other hemorrhages occur, enormous swelling of the gums and necrosis of the jaw take place, and death, usually from intercurrent pneumonia, finally comes as a blessed release. Occasionally death takes place very suddenly and unexpectedly; Follis (1942) pointed out the possible importance of vitamin C deficiency in producing cardiac hypertrophy and insufficiency. In infants the symptoms are: pallor; arrest of growth and loss of weight; poor appetite; livid, swollen gums which bleed easily; and pain. This pain is manifested by a worried expression, a whimpering cry and eversion of the thighs which are flexed on the abdomen. The most tender point is at the lower end of the femur. The pain in both infants and adults is caused by subperiosteal hemorrhages; in the former, in addition, there may be separation of the epiphyses and even fractures. In both infants and adults marked anemia, usually of the hypochromic-microcytic (iron-deficiency) type, is generally, but not invariably, present. In two of three patients in whom bone marrow biopsies

were performed, Israels (1943) found evidences of a depression of erythropoiesis rather than a failure of maturation at any particular stage. A number of cases of intracranial hemorrhage have been reported. Scott (1936) recorded a case of atypical scurvy in a girl of fourteen years whose only presenting symptom was a spontaneous subaponeurotic hematoma which gave her the appearance of having ordinary hydrocephalus.

Scurvy was unmistakably described by Jacques de Vitry in the forces of the Crusaders who were besieging Damietta in 1218, but earlier reference to the disease has not been discovered, unless a doubtful passage in Hippocrates be accepted. Always, at least since the Middle Ages, it has ravaged armies and beleaguered cities, and when long sea voyages began to be made it quickly struck at the crews of vessels; Hofmeyr (1941) has interestingly recounted how, in 1652, the Dutch made their first settlement at the Cape of Good Hope for the express purpose of supplying fresh fruits and vegetables to the scurvy-ridden crews of ships engaged in passage between Europe and the Far East. In passing, it may be of interest to note that the lime juice with which the British Navy rid itself of scurvy after 1795, and incidentally won for its crews the undying soubriquet of "limeys," was not lime juice at all but only the juice of the humble and far less exotic lemon. Nowadays expeditions to far-off places are protected by nothing more romantic than crystals of ascorbic acid. Scurvy caused severe losses in certain areas during War I, being especially destructive among the British troops who were besieged at Kut-el-Amara. Then, during the interim of partial and precarious world peace, the disease seemed to be endemic among adults in northern Russia and China and certain parts of the tropics, in the latter region occurring principally, according to Manson-Bahr (1940), among coolie gangs recruited for labor purposes and placed on a dietary of dried cereals and preserved foods. Doubtless, however, as shown by the studies of McDevitt *et al.* (1944) in Newfoundland, severe grades of vitamin C deficiency might have been found in many regions for the looking. Now, with the planet being ravaged once more in War II, scurvy will doubtless take a very high toll again. Here in the United States, and elsewhere in lands not under the plunderer's heel, it has for a long time existed principally as a problem in infant feeding, though during the depression years sporadic cases were reported among adults upon whom the disjointed times forced semistarvation in the midst of plenty. Meulengracht several years ago drew attention to the fact that scurvy is also not to be overlooked in unmarried individuals who live alone and prepare in their own rooms a diet that is nearly always deficient in the items of meat, fruits and vegetables; a number of recent reports, confirming the contention, have also shown the possibility of scurvy appearing during the course of special dietary regimens enforced during severe gastro-intestinal disturbances or taken as a matter of choice by eccentric individuals. The fine study of Lund and Crandon (1941) also indicated the advisability of investigating the dietary history of patients coming to major surgery since marked vitamin C deficiency delays or even prevents wound healing.

A few years ago, the newer methods of studying vitamin C levels—capillary strength tests and direct titration of ascorbic acid in blood, spinal fluid and urine—were looked upon as great aids in the detection of subclinical scurvy. However, since such tests, particularly that of the level of the acid in the blood, have shown large numbers of children to have very low vitamin C levels without evidences of clinical scurvy, some investigators are beginning to question

the significance of such findings; but Sebrell (1943) summarizes the matter by saying that such findings at least indicate an intake of vitamin C below that necessary to maintain the body reserves at the highest level. The newest method of determining the vitamin C status of a patient is through use of the ascorbic acid saturation test. The patient is given 200 mg. of ascorbic acid in water by mouth or in saline solution slowly injected intravenously, and the excretion of the acid in the urine is then determined. The test is based upon the assumption that the more depleted the tissues are of ascorbic acid the larger amount of the administered agent they will retain and therefore the lower the excretion in the urine. According to Engelfried (1944) an excretion of less than 10 mg. of ascorbic acid in six hours can be definitely considered to indicate an inadequate intake of vitamin C in the diet.

THERAPY

Dietetic Treatment.—Scurvy may be easily cured simply and solely by the addition to the diet of a sufficient amount of the antiscorbutic factor. Unpasteurized milk and raw meat contain this factor, but either must be taken in very large quantities in order to suffice (Stefansson, 1939, to the contrary, who claims that Eskimos remain free of scurvy on well-cooked meat); fresh vegetables, especially cabbage, turnips, green peppers, baked sweet or Irish potatoes, and tomatoes best serve the purpose. Orange or tomato or pineapple or grapefruit juice are excellent; lime juice is less effective and grape juice and cider or apple juice are hardly effective at all. These fruit juices, *i.e.*, two or three oranges or lemons daily (or the same number of bananas), or somewhat more than equivalent quantities of the canned juices, or the liberal use of fresh vegetables not too long cooked, will very rapidly cure a case of scurvy.

Ingalls (1939) says requirements are met by 50 cc. of orange juice, or 150 cc. of tomato juice, or 250 cc. of pineapple juice daily, but immensely much more than this must be used in severe cases. It is best in preparing the juices at home to use only glass or china receptacles as iron and copper rapidly destroy the vitamin; after more than two days of refrigerator storage fresh juice depreciates considerably even if covered. Stale vegetables are of little value, and fruits and vegetables preserved by artificial drying are practically worthless. By new processes it has now become possible to can fruits and vegetables without destroying completely the antiscorbutic factor; the quick freezing process also preserves some of the vitamin; the commercial vogue for quick ripening by ethylene is apparently not harmful. In many instances past and present ingenious persons and even large populations have saved themselves from scurvy by drinking copiously of a tea brewed from pine needles.

The disease is prevented by the same measures which suffice for cure. In the case of infants that are not being nursed by mothers *who are taking liberal amounts of antiscorbutic foods, since both the fetus and the suckling infant drain the mother's supply*, the vitamin factor must be artificially supplied after the first two weeks of life.

Somehow, perhaps by reason of the recent advances in our knowledge of the part that sunshine plays in the cure of rickets, the notion has spread that scurvy, too, is amendable to prevention and cure by the ultraviolet rays, and that irradiation of foods increases their antiscorbutic properties. There is absolutely no warrant for this belief.

Ascorbic (Cevitamic) Acid.—In 1928, Szent-Györgyi isolated hexuronic acid from the suprarenal gland and concluded that it is identical with the reducing

substance in active vitamin C concentrates. The first definite identification of the substance as vitamin C was made by Waugh and King in 1931, published in 1932. It is currently prepared from adrenal glands, and from citrus fruits, cabbage, peppers, and other plant sources, and is also produced synthetically. The Council-accepted (1944) ascorbic acid is available in the form of crystals, in capsules, tablets and ampules of solution. The preventive dose for infants is 10 mg. daily (though many pediatricians nowadays use 25 mg. routinely) and the therapeutic dose 30 to 50 mg.; for the adult these doses are 25 mg. and 100 to 300 mg. respectively. Since, however, there is no evidence that this vitamin is harmful in any reasonable quantities, it is a not infrequent practice to give ten times these curative doses in severe cases; part or all of this may be given intravenously dissolved in 10 cc. of sterile distilled water or sterile physiologic saline solution, injecting slowly—the only record of a reaction I have seen is that of Anderson and Leake (1935); chill, fever and general discomfort in a patient given 100 mg. of the drug. My feeling is that in time such high dosage will be abandoned as unnecessarily expensive except in obviously moribund patients.

Treatment of Anemia.—This matter is discussed in the section on Anemias.

PELLAGRA

When this disease develops severely and is untreated by the newer methods, its four outstanding features, which will serve to fix the characteristic picture in mind, are dermatitis, diarrhea, dementia and death. All of these symptoms need to be somewhat elaborated upon of course. The dermatitis is sharply defined, is nearly always symmetrical (Bean *et al.*, 1944, found only 32 instances of unilateral distribution in 889 cases), and is confined to those areas of the skin which are exposed to light, *i.e.*, the face and neck, the backs of the hands and the lower parts of the forearms, the feet and the lower legs. The term "diarrhea" is used to indicate an outstanding feature of a large proportion of the severe cases, though there is nothing characteristic of either the accompanying abdominal pain or of the stool except that the latter is usually foul and watery (vaginitis, urethritis, and endocervicitis are also frequently present). More or less severe stomatitis, glossitis, gingivitis, pharyngitis, gastritis, achylia gastrica and enteritis are prominent features in most cases. The nervous symptoms which are so serious a part of the pellagra syndrome are so many and so varied that to them as a whole may perhaps be applied the appellation "neurasthenic manifestations"; but it is significant that Lewy, Spies and Aring (1940), studying 50 patients with the classical type of the disease, found that 75 per cent had polyneuropathy of the motor and sensory nerves; 20 per cent had extrapyramidal signs, of which one half showed mild Parkinsonism; and 12.5 per cent had tremor and pyramidal tract signs. Among the cases of pellagra which appeared in great numbers in Hong Kong just prior to its capture by the Japanese, Wilkinson and Au King (1944) found a number of cases of amblyopia which cleared under antipellagra therapy. In advanced cases true dementia simulating any of the well-recognized psychoses not infrequently develops. Death I have set down as an outstanding feature of the disease, and so it was in patients who became definitely bed-ridden in the days before the development of more or less specific vitamin therapy; in those who suffer only

from a mild annually recurrent attack of the disease in an endemic area the mortality is quite low even without treatment.

In recent years a few cases of pellagra have been reported in association with the symptoms of Addison's disease. In his fine monograph on pellagra, Seale Harris (1941) says that heart complications occur relatively infrequently. However, Rachmilewitz and Braun (1944) report two cases in which the electrocardiographic changes were reversed through the administration of niacin (nicotinic acid). Moore *et al.* (1944) have called attention to the macrocytic anemias which occur in some patients with pellagra (see the section on the Anemias).

The first published account of pellagra was that of Casal, in Spain, in 1735. Shortly thereafter it was recognized as a widespread malady in northern Italy, where it was exhaustively studied by Strombio in 1786–1789. At the present time it is quite prevalent in southern Europe and the Balkan States, Poland, Asia Minor, Transcaucasia, India, Japan, China, Korea, Manchukuo, Egypt, the Sudan, Algeria, Tunis, the Red Sea coast and many regions throughout Central, West and South Africa, the West Indies, Central America and the southern United States. Doubtless the disease can be found elsewhere for the looking, as has already been demonstrated in Canada, the British Isles, Belgium, Denmark and Germany. It is probably only lack of recognition of the entity which prevents the reporting of more cases from Malaya, Australia and the mid-Pacific islands. In the northern United States, sporadic cases had been seen as early as 1863 but its existence as a serious endemic malady in the South was not recognized until 1906. In the endemic areas throughout the world pellagra is principally a disease of the poor whose diet is faulty; but sporadic cases are seen everywhere in individuals of all economic classes. Practically all of these latter patients are deprived of the necessary antipellagric vitamins through one or a combination of several of the following factors: "finickiness" in eating, addiction to dietary faddism, chronic alcoholic addiction, a prolonged illness with poor alimentation or a relatively short illness with high fever, gastro-intestinal pathology interfering with alimentation or absorption, pregnancy. (Bean *et al.*, 1944, find childbearing and its inherent complications more often than any other factor predisposing to pellagra in populations whose diet is near the borderline of inadequacy.) In a very few instances, apparently associated with an excessively high vitamin requirement, an individual is seen who develops the disease even though eating and absorbing a balanced diet. It is suggested that the reader study the section on Subclassical Deficiency States.

Pellagra occurs in persons of all ages; blacks and whites, and probably all other races, are equally stricken. In the endemic areas of the South cases make their appearance principally in the spring and persist until the middle of the summer. The disease "kwashiorkor," encountered by Williams (1935) in Accra on the Gold Coast, was believed by Stannus (1936) to be merely pellagra in children, but Brown and Trowell (1944) seemed to be not quite certain on the point; Spies *et al.* (1939) have shown here in the United States that in an area in which pellagra is endemic the disease is common among infants and children.

THERAPY

The chemical breakup of vitamin B_2 into its constituent parts, the principal of which are niacin (nicotinic acid), riboflavin, pantothenic acid and pyridoxin (vitamin B_6), and numerous unidentifiable fractions, has supplied the means

for finally proving that pellagra is a vitamin deficiency disease. But Rhoads (1939) has well pointed out that these recent triumphs should not cause us to forget that Goldberger discovered the cure for pellagra a good many years ago through demonstration of the following things: (*a*) that inadequate diets were uniformly eaten by human beings who contracted pellagra; (*b*) that such diets fed to experimental animals caused a similar disease in them; (*c*) that liberal diets were curative in both the spontaneous and experimental diseases; (*d*) and finally, that pellagra could be caused in human volunteers by feeding them deficient diets which caused the disease experimentally in animals. And the central fact in the above summary of Goldberger's findings is still true, *i.e.*, a deficient dietary is the cause and an adequate dietary the cure of pellagra. Even today, when by proper employment of the several fractions of vitamin B_2 arrest and apparent cure of the disease can often be accomplished without a change in dietary, it is nevertheless the burden of the testimony of the leaders in this field of study that a return to an adequate dietary is the thing to be chiefly desired not only for permanent cure of pellagra itself but also because the diet of pellagrins is one which practically always causes other deficiencies as well. The problem of pellagra in the endemic areas is an immensely complex one involving questions of food habits, food supply, living habits, money and many other things which determine the scale of living, but it is a heartening thing to learn from Kooser and Blankenhorn's (1941) study that even in a community in which economic betterment had not taken place a long campaign in the health-sparing value of foods could be highly successful. They compared two adjacent neighborhoods with similar economic status in the mountain counties of Kentucky. The one which got rid of pellagra had learned to have gardens, cows and chickens, and the one which still suffered pellagra had only insignificant gardens and the local grocery stores as sources of food. There was not much difference in consumption of the pellagra-producing diet, *i.e.*, both groups ate corn meal and fat pork in about equal amounts, but in the consumption of pellagra-preventing foods there was a significant difference in that the group which freed itself of pellagra ate more fresh milk, lean pork, eggs and chickens.

The Use of Food in Therapy.—When treatment of a case of established pellagra is undertaken the essentials of the dietary to be enforced may be condensed from the studies of Spies and his associates into the following: a well-rounded diet of 4500 calories, rich in meat, liver (perhaps this item should be especially stressed), eggs and milk.

Dried Brewers' Yeast.—This agent is very frequently used to supplement the full diet described above which unfortunately it is often difficult to obtain for the pellagrin or to persuade him to eat. De Kleine (1942) says that of the various factors contributing to the marked reduction in pellagra mortality in the South in recent years, none has been more important than dried brewers' yeast, though Remington (1944) felt it not easy statistically to substantiate this statement. The amount usually administered in a full-blown case, if the patient can be got to take it, is 75 to 100 Gm. daily. One manufacturer makes the following suggestions for palatably mixing one level teaspoonful (2.5 Gm.) of this powder: (1) shake in cocktail shaker with 4 ounces of milk (with or without 1 level teaspoonful of sugar and cocoa); (2) stir with fork into $\frac{3}{4}$ ounce of catsup or chili sauce—optional, add a few drops of lemon juice; (3) stir with fork into 3 ounces of soup (preferably thick soup such as bean, pea, oxtail, beef, etc.); (4) spread on bread with two to three times the amount of

peanut butter; (5) add 1 level *tablespoonful* (and a little extra salt) to two cups of meat stock gravy. Several years ago Spies described his very satisfactory use of a peanut butter-yeast mixture: 75 per cent of peanut butter and 25 per cent of a special "C–50" strain of relatively palatable yeast supplied to him by the research department of one of the large breweries. The patients ate this mixture *ad libitum* at two of the daily meals, consuming an average of 60 to 75 Gm., in some instances as much as 160 Gm., per day. This mixture contains niacin (nicotinic acid), riboflavin and thiamine, and per unit weight as much carbohydrate as potatoes, more protein than steak, and one-half as much fat as butter. This yeasted peanut butter mixture can be bought as "honey peanut butter" from the Andrus-Scofield Company, Columbus, Ohio, and is locally procurable in many places. N.N.R. (1944) contains brewers' yeast powder and brewers' yeast tablets.

The Use of Vitamins in Therapy.—When dietary correction cannot be made, or when there is reason to believe that some degree of subclassical pellagra exists in spite of the taking of an ordinarily adequate diet, or when the patient is very ill and it is necessary to accomplish arrest and cure of the condition as quickly as possible, under these conditions resort should be had to employment of vitamins in pure form. Since the showing, by Elvehjem and his associates, in 1937, that niacin (nicotinic acid) is effective in curing experimental canine pellagra, and the dramatic improvement in many of the symptoms in the human form of the disease, first reported by Fouts *et al.* in the same year and subsequently by many observers throughout the world, this vitamin has been accepted as the specific curative agent in pellagra. The improvement effected by its use is undoubted and often dramatic, but such leaders in the clinical phases of this work as Spies and Sydenstricker find that all symptoms are not always caused to disappear in all cases; that indeed thiamine (vitamin B_1) therapy is necessary to clear the neuropathic part of the picture; and that sometimes riboflavin must also be used and in an occasional case even pyridoxin (vitamin B_6). In short, pellagra is a disease in which the outstanding deficiency is in niacin (nicotinic acid) but the other elements of the B_2 complex, riboflavin and pyridoxin, may also be deficient, and furthermore a deficiency in B_1 (thiamine) is often associated with if not integrally a part of the pellagrous picture. The use of niacin (nicotinic acid) alone will be described here because the other agents are elsewhere discussed: thiamine in Beriberi, riboflavin in Ariboflavinosis, pyridoxin in Pyridoxin Deficiency.

Niacin (Nicotinic Acid) and Niacin Amide.—The studies of Sydenstricker and Spies and their associates have shown that the amount of niacin (nicotinic acid) requisite for cure or maintenance is seldom predictable. Elvehjem (1940) placed the normal requirement at about 25 mg. daily, and it seems that a few patients with mild pellagra can be cured with this dose, "though slowly," according to Sydenstricker (1941). Increasing the dose to 300 to 500 mg. usually induces cure of the glossitis, stomatitis and diarrhea in about two days; the mild psychic disturbances disappear even more rapidly, though one to two weeks is often required for clearing of the cutaneous lesions. In very severe cases it is often necessary to give as much as 1000 mg. for a few days, but in any type of case it is customary to reduce the dose to 100 to 150 mg. daily after marked improvement has begun. After cure has been accomplished maintenance dosage is usually not required if the patient is able to obtain an adequate diet, otherwise the requirement varies with patients from 25 to 100 mg., occasionally even more.

Niacin (nicotinic acid) is usually given in tablet form by mouth; when relatively small doses are given it may be taken two or three times daily after meals, but when larger doses are necessary it is customary to give divided doses many times throughout the day—for example, 10 tablets of 50 mg. each are spaced about an hour and a half apart in order to get in 500 mg. during ordinary waking hours. A variable proportion of patients experience a reaction characterized by flushing, burning and itching sensations with increased temperature of the skin upon large dosage, the reaction subsiding after a little while and usually not being severe enough to be of any moment when dosage is spaced throughout the day. The pulse, blood pressure, respiration and electrocardiogram are usually not affected during the reaction. Field and Robinson (1940), confirming the experience of Spies and others, found that nicotinic acid amide, used in the same dosage as nicotinic acid itself, does not cause these reactions; the amide is fully as effective as the acid, indeed it is probably in the converted form in which the acid is active in the body.

When necessary niacin (nicotinic acid) or the amide may be given intravenously or intramuscularly. N.N.R. (1944) contains ampule solutions of nicotinic acid carrying from 1 to 10 mg. per cubic centimeter and ampule solutions of the amide containing 20 to 100 mg. per cubic centimeter.

Reactions other than the flushing above described have been occasionally noted in isolated instances: nausea, vomiting, epigastric distress, throbbing, palpitation, dizziness, urticarial rash; all have been transient though sometimes distressing; I do not believe that such reactions have followed the use of the amide preparation.

NICOTINIC ACID DEFICIENCY ENCEPHALOPATHY

Jolliffe *et al.*, in 1940, reported an interesting series of 150 cases of an encephalopathic syndrome characterized by clouding of consciousness, cogwheel rigidities of the extremities and uncontrollable grasping and sucking reflexes. This syndrome may occur alone or in association with manifestations of other deficiencies such as pellagra, beriberi and scurvy. Sydenstricker (1943), and Gottlieb (1944), have confirmed these findings, each in a smaller series of patients. Patients with this malady treated by hydration alone or plus thiamine almost invariably die; patients treated by hydration plus substances rich in the vitamin B complex such as brewers' yeast and liver show a moderate drop in mortality; but when these patients are treated by hydration plus nicotinic acid a marked drop in their mortality results. Jolliffe believes it is permissible to look upon the pellagra syndrome as representing only a partial deficiency of nicotinic acid of sufficient duration to produce the structural changes recognizable in the clinical picture of pellagra, but that in the encephalopathy under discussion practically complete nicotinic acid deficiency develops so rapidly that there is no time for the development of the pellagrous picture.

THERAPY

Sydenstricker (1943) says that very large amounts of nicotinic acid (niacin) are required during the first few days of treatment. He customarily gives 100 mg. of nicotinic acid or 30 mg. of nicotinamide every hour for ten hours during the first two days, continuing this dosage longer if necessary. Where coopera-

tion is not obtainable the vitamins must be added to intravenous or subcutaneous infusions or be given intramuscularly. The majority of patients are said to show great improvement within forty-eight hours after treatment has been started, and once this improvement is definite the daily doses of nicotinic acid can be reduced to 500 mg. and of the amide to 150 mg. Later the oral administration of 25 mg. of nicotinic acid three times daily usually suffices for maintenance. Gottlieb (1944) feels that half Sydenstricker's dosage would be adequate in most cases though agreeing that when the full picture is developed the full dosage should be given. Both he and Sydenstricker feel that thiamine should be given as well as nicotinic acid. Sydenstricker uses the empirical rule of giving one-tenth as much thiamine as nicotinic acid; he says that this is probably wasteful but seems effective. He also favors the addition of dried brewers' yeast, 15 to 30 Gm. daily, to the diet regardless of the amounts of the crystalline vitamins that have been given.

ARIBOFLAVINOSIS

(*Including the Oro-Genital Syndrome*)

In 1938, Sebrell discussed the possibility of clinical pellagra being a multiple deficiency and pointed out that riboflavin deficiency might occur in man simultaneously with, or independently of, pellagra. He therefore set about studying the matter, and in the same year he and Butler reported that 13 out of 18 patients to whom they gave a special diet low in riboflavin content developed the symptoms we now recognize as characteristic of ariboflavinosis; furthermore, these symptoms disappeared following the administration of synthetic riboflavin, reappeared following its discontinuance, and again disappeared following riboflavin therapy. Adequate confirmation of these findings soon appeared and we now recognize this newly discovered vitamin deficiency as an important and widespread malady. The disease occurs in all age groups, but Spies *et al.* (1940) are convinced that among malnourished children in the South it occurs more frequently than any other deficiency syndrome; Sydenstricker *et al.* (1940) say it is possibly the most prevalent, without any age limitations, of all the apparently uncomplicated avitaminoses—Goldsmith's (1943) finding of a 34 per cent incidence in 200 consecutive admissions to the medical services of the Charity Hospital, New Orleans, certainly supports this viewpoint. It has therefore been very surprising to find Cayer *et al.* (1945) saying that it is uncommonly seen in their clinic at Duke University. The disease has been reported in England and appears to be widespread in India, China, Malaya and Africa.

Many of the symptoms of which the victims of this disease complain are characteristic of all the vitamin deficiencies, namely, weakness and easy fatigability, anorexia, gastric discomfort and insomnia, but the diagnostic signs of specific ariboflavinosis are the reddened macerated areas at the angles of the mouth known as "cheilosis," scaly-greasy lesions in the nasolabial folds and on the alae nasi and ears, a specific glossitis in which the tongue is roughened and fissured and purplish-red or magenta in color instead of scarlet as in nicotinic acid deficiency, a tendency for the appearance of a "shark-skin" type of eruption and seborrhea which may be very extensive, pruritus ani and vulvae, and finally ocular symptoms characterized by circumcorneal injection and

corneal vascularization, lacrimation, burning of the eyes, mydriasis and disturbances of accommodation, and failure of vision especially in dim light. In one third of the cases of Sydenstricker *et al.* (1941) there were changes in the appearance of the iris, and this group of investigators believe that at least one of the varieties of keratitis, that known as rosacea keratitis, is really the corneal vascularization of riboflavin deficiency. In India it has become customary to recognize an "oro-genital" syndrome consisting of angular stomatitis, glossitis and scrotal dermatitis, which may not be Simon-pure ariboflavinosis. And as a matter of fact, the studies of Boehrer *et al.* (1943), Machella and McDonald (1943), and Stannus (1944), and even of earlier investigators, indicate that here in the United States as well as elsewhere the classical symptoms are not always presented as a result of deficiency in riboflavin solely.

Though due in the vast majority of instances to the taking of an inadequate diet, ariboflavinosis is undoubtedly sometimes the result of gastric achlorhydria which prevents the extraction of riboflavin from foods or permits its destruction in a medium of low hydrogen ion content. Stephenson (1942) reported a case of possible ariboflavinosis appearing on the thirteenth day of life in a prematurely born baby. Ellenberg and Pollack (1942) reported an interesting group of 34 cases of a disorder that they took to be ariboflavinosis but which proved unresponsive to riboflavin therapy; however, none of these patients had ocular or seborrhea-like lesions, and further intensified study revealed that the labial and lingual disturbances resulted from ill-fitting dentures.

THERAPY

Sebrell *et al.* (1941) present data indicating that the daily intake of 3 mg. of riboflavin is sufficient for a normal adult. In the experience of Sydenstricker *et al.* (1941), 5 mg. has been the average amount required for rapid cure of the deficiency syndrome; in the presence of achlorhydria, diarrhea, or severe hepatic disease, 10 to 15 mg. may be required. The drug is available in tablets, capsules and ampules for parenteral administration. Butler (1943), of Sebrell's group, says that where there are evidences of impaired absorption or inadequate utilization, good response will be obtained by the twice daily intramuscular injection of 5 mg. In India, Mitra (1943) effected cure in from twelve to seventeen days in 16 of 18 patients with the oro-genital syndrome whom he gave 5 mg. daily by mouth; the 2 resistant cases cleared within five days when changed to 3 mg. of riboflavin plus 100 mg. of nicotinic acid (niacin). Spies and his group found their cases responding to either riboflavin, brewers' yeast, or liver extract, and both he and Butler stress the importance of getting these patients onto a diet which will supply plenty of the B complex: liver, lean meat, milk, eggs, whole wheat or enriched cereals, and the highly colored vegetables.

No toxic reactions following riboflavin administration have been reported in man.

PYRIDOXIN (VITAMIN B_6) DEFICIENCY

Since 1939, Spies *et al.* have reported 24 cases in which there were residual symptoms of nutritional deficiency which could not be relieved with nicotinic acid, thiamine, or riboflavin, but which rapidly cleared up following the administration of pyridoxin (vitamin B_6). Smith and Martin (1940) have also re-

ported 4 cases of cheilosis, which is a part of the ariboflavinosis syndrome, which cleared as well under pyridoxin as under riboflavin. Nothing very definite is known as yet regarding this deficiency except the above-stated facts. The relatively recent literature contains a number of reports of the trial of pyridoxin in various neuromuscular and dermatologic disturbances, but in no instance are the results impressive.

BERIBERI

In recent years great strides have been made in our understanding of this disease which is now known to be due to thiamine (vitamin B_1) deficiency. It seems to me that, from the practical standpoint, the entity can be divided into three distinct types: classical, subclassical and infantile beriberi.

Classical beriberi of the "mixed" type is characterized by peripheral neuritis, edema, myocardial weakness and enlargement of the heart. The attack usually begins slowly with malaise, palpitation and shortness of breath, gastro-intestinal disturbances and edema which usually begins in the pretibial region. Then begins the multiple peripheral neuritis, which is associated with soreness of the muscles, with areas of paresthesia and superficial anesthesia, and with diminution or loss of the deep reflexes. The edema spreads up the legs, effusions appear in the serous cavities, ataxia or a marked steppage gait becomes pronounced, or flaccid paralysis with muscular atrophy appears; the heart, especially the right side, becomes greatly enlarged, and the patient dies from myocardial failure due to hydropic degeneration, death coming usually after an illness of several months although demise with few or no prodromal symptoms is not rare. The observations of Porter and Downs (1942), bearing out those of earlier observers, indicate that in the circulatory failure in beriberi there may be an increased cardiac output, a low arteriovenous oxygen difference, an elevated venous pressure and a shortened circulation time; therefore, when recovery occurs though it doubtless results from an increased efficiency of the myocardium there is likely also an element of increased arteriolar tone. Pathologically the disease is characterized by degenerative changes in the peripheral nerves and also in the anterior and posterior ganglia of the cord. There are also occasional disintegrative changes in the brain cells, though mental symptoms to correspond are very rare.

A "wet" type of the disease is frequently differentiated from a "dry" type, *i.e.*, in the former the edematous phenomena predominate over the apparent nervous system changes, whereas in the latter the reverse is true. It is said that references to this classical type of beriberi are contained in very ancient Chinese and Japanese manuscripts, but Wilder (1943), after studying translations of the early literature, is doubtful of the authenticity of these early cases. At present the disease is endemic in Japan, China, Indo-China, the Straits Settlements, the Netherlands Indies, the Philippines, Newfoundland, Labrador, and Iceland, and here and there in India ("beriberi" in Singhalese, the native language of Ceylon, means "I cannot"), the West Indies, South America and some parts of "native" Africa and Australia. To what extent beriberi has developed among the populations enslaved during War II is not as yet a matter of record, but Adolph *et al.* (1944) stated authoritatively that

beriberi and other syndromes due to insufficiency of the vitamin B complex were the most prominent of the nutritional disorders occurring among the Americans and Canadians imprisoned by the Japanese.

It was Takaki who first proved by his dietary readjustment in the Japanese Navy, in 1883, that beriberi is caused by a food deficiency. He held that it was protein that was lacking in the diet, but the observation of Eijkman, in 1896, that a polished rice diet always caused the disease, and the subsequent researches of many investigators, have shown that the missing substance is vitamin B_1, which has been isolated and synthesized as thiamine. This substance is concentrated in the outer layers of the cereals, especially rice, that are used for food by the native populations of large areas in the tropical and subtropical regions all around the globe; furthermore, it is removed by modern milling processes, and therefore peoples who subsist during certain portions of the year almost exclusively upon this polished rice suffer from the deprivation of vitamin B_1; that is to say, they develop beriberi. It is a mistaken idea, however, that rice eating alone will cause the disease, for it follows also upon a prolonged period of the monotonous eating of other completely milled cereals, such as wheat or corn, or such a diet as white bread, molasses, sugar and fats. Likewise, too exclusive reliance upon canned food invites the disease. In Europe and North America occasional outbreaks of classical beriberi occur in faultily managed institutions, but the number of cases is usually not large before proper dietary adjustment is made. However, in 1903, Young, and later Scott and Herrmann (1928), called attention to the fact that the "maladie des jambes" of the rice growers of Louisiana is beriberi. We are now aware also that the disease occurs sporadically with fairly high frequency throughout the whole United States and needs only to be looked for to be found, the victims in these instances being individuals who, for one of the following reasons, ingest a diet deficient in thiamine: chronic alcoholics, who not only substitute liquor for much of their food but also require thiamine to metabolize the alcohol, and who are also likely to have gastro-intestinal disturbances which interfere with absorption; the pregnant woman, whose metabolic requirement (and hence thiamine requirement) is increased by gestation, but who may nevertheless severely restrict her diet because of nausea and vomiting; patients with any type of gastro-intestinal disturbance which limits ingestion, retention, or absorption of food; the use of severe elimination diets because of food sensitivities; febrile diseases in which increased metabolic requirement is accompanied by anorexia; possibly thyrotoxicosis in some instances; cirrhosis and other liver derangements which seem to inhibit utilization of thiamine; perhaps severe parenchymal damage to any internal organ may raise thiamine requirement; maintenance of a patient exclusively on intravenously or rectally administered dextrose solution; and probably in a few instances there are individuals whose thiamine requirement is higher than can be obtained from a normal dietary. Waring (1928) recorded the occurrence of beriberi in a two months' old infant and Roscoff (1942) in one of four months; in Van Gelder and Darby's (1944) case the infant was born with severe, almost fatal manifestations of beriberi. Roscoff pointed out that beriberi may underlie some of the deaths at present attributed to status thymicolymphaticus or cases diagnosed as idiopathic cardiac hypertrophy.

Subclassical beriberi is a term which I am applying to a type of thiamine deficiency which has little in common with the classical form of the disease since its manifestations are more nearly those to which the term "neuras-

thenia" may properly be applied. I think that Willie (1940) probably expressed the feeling of many psychiatrists when he said that the neuropsychiatric implications of thiamine deficiency is a subject which is still in the uncrystallized stage, but it seems to me that Williams (1941) and his coworkers have clearly shown through carefully controlled thiamine-deprivation studies that evidences of thiamine deficiency can be recognized far short of the classical signs and symptoms of beriberi. Their patients, who were carefully selected and cooperative throughout, manifested several or all of the following signs or symptoms: capriciousness of appetite sometimes going to the point of intolerance for food; low blood pressure and faint cardiac sounds; marked sinus arrhythmia, palpitation and a pulse rate exceeding normal limits on moderate exertion; giddiness associated with pallor on standing; anemia of a hyperchromic, macrocytic type; lowered basal metabolic rate; intolerance to cold; changes of behavior, the subjects becoming in most instances depressed, irritable, quarrelsome, fearful, and inefficient through confusion in thought, uncertainty of memory and loss of manual dexterity; headache, backache, dysmenorrhea, soreness of muscles, gastric distress after meals, sleeplessness, tenseness, paresthesia, intolerance to noise and increased sensitivity to painful stimuli. Studies similar to those of Williams have been performed also by Jolliffe *et al.* (1939), with similar findings. And the amazing and important thing about both these investigations is that the diets employed were of about the quality that a shockingly high proportion of our populace is accustomed to employ routinely. The inescapable conclusion—a thesis already elaborated by Jolliffe several years ago—is that the incidence of subclassical beriberi must be high in our land.

Infantile beriberi has long been recognized as a dreadful scourge in the Far East for the incidence is high and the death rate apparently over 90 per cent. It is a disease of breast-fed infants whose mothers are thiamine deficient. Methylglyoxal has been isolated from the milk of such women, and Fehily (1943), formerly of Hong Kong where she made a considerable study of the disease, apparently feels convinced that the death of these infants, which often occurs quite suddenly, is due to poisoning by methylglyoxal imbibed in the milk.

THERAPY

Thiamine.—The use of the specifically deficient agent, thiamine hydrochloride, has of course revolutionized the treatment of beriberi; its employment effects a dramatic alteration in the patient's condition, and progress thereafter is steady and rapid to recovery. Present dosage tends to err on the side of wasting the drug rather than risking the giving of too little, since, while it is generally presumed that 2 to 3 mg. cover the daily adult needs in health, there has accumulated little evidence as yet to indicate how much increase is required to overcome a long-standing deficiency. In fulminating cases it is the practice of most men of large experience to give the first few doses intramuscularly, subcutaneously, or even intravenously. Weiss (1940) uses 20 to 30 mg. three times daily; in some urgent cases Jolliffe and Rosenblum (1939) have used as much as 1000 mg. in the first twenty-four hours. After the patient is saturated with thiamine (the urine acquires a burnt rubber odor) dosage may be reduced to a much smaller amount, such as 5 to 10 mg. daily. As a matter of fact, I imagine increasing experience is going to show that doses larger than this are probably rarely necessary at any time; Jones and Bramwell's (1939) patient was in extremis but he was given only one daily intra-

muscular injection of 2 mg. of thiamine, and he lost the signs of heart failure in five days and was discharged cured in seventeen days, the total thiamine dosage having been only 30 mg. Mills (1941) has mentioned a few cases of patients who developed symptoms resembling those of hyperthyroidism apparently as a result of thiamine therapy; cessation of the drug was followed by prompt disappearance of these symptoms. Laws (1941), Schiff (1941), and Stein and Morgenstern (1944) have each reported a case in which an anaphylactic type of reaction occurred in a patient apparently sensitized by repeated injections of thiamine; Mitrani's (1944) patient presented an eruption after the first as well as all succeeding injections of thiamine. There would seem to me to be no reason to use the drug parenterally in the vast majority of instances since tablets of various sizes are available for oral use and prompt improvement is the proof of gastro-intestinal absorption; in any case the performance of an intradermal test before injecting would seem the part of wisdom. Klopp *et al.* (1943) have found that in many instances the administration of thiamine is followed by an unexplained transitory increase of riboflavin excretion in the urine.

Supplementary B Complex.—Wilder (1943) doubtless expresses the consensus when he says that in addition to thiamine the vitamin B complex as a whole should be provided; he suggests the daily injection of a concentrated liver extract in 3 cc. doses, or otherwise the giving of dried brewers' yeast by mouth in doses of 45 to 60 Gm. a day.

Diet.—The dietary requirements for the correction and the prevention of recurrence of beriberi are the following, according to Jolliffe and Rosenblum: When the patient is extremely ill, limit the diet to milk, eggs, ground liver, puréed legumes, thin whole wheat cereals, and fruit juices, administered if necessary through a nasal catheter. Following improvement, or in less severely ill patients, whole wheat bread should be added, the legumes need not be puréed, other vegetables and raw whole fruit should be added, and a wider variety of meats permitted with substantial portions of either liver or pork muscle included in one of the meals daily. All vitamin-free foods such as unfortified white bread, pastries, alcohol, corn syrup, candy, corn starch and soft drinks should be eliminated from the diet, and vitamins other than B_1 added if they seem indicated.

NUTRITIONAL EDEMA

This is a beriberi-like state which was distressingly prevalent in the blockaded countries of central Europe during War I. During the present nutritional crises in Europe and in China incident to War II, Sebrell (1943) says we may be certain that the incidence of nutritional edema is extremely high although no accurate figures are as yet available. Laycock (1944) has already given us a picture of this entity as he saw it in Chinese prisoners who, after a period of deliberate and systematic starvation by the Japanese in occupied China, were then released into free China. In patients suffering from this malady there is edema of variable grade and complaint of weariness and easy fatigability; the total protein and albumin of the blood serum are below normal, but the heart is not enlarged and polyneuritis is not a characteristic symptom. This illness

results from living on a diet containing insufficient protein and too much fluids and salt. Precisely how much nutritional edema there is in the world during times of relative peace, and how much of the alleged beriberi is truly this entity, is not definitely known, but presumably the incidence is very high in those regions where chronic undernutrition obtains among the masses. Isolated cases were reported in all the more advanced countries during the economic slump which preceded War II. Cases are also seen accompanying some malady in which sufficient intake or utilization of protein foods has been impossible. Epidemic dropsy, which occurs principally in restricted areas in India, and is now known to be due to an adulterant of mustard oil used in the preparation of food, is not to be confused with this entity.

THERAPY

The chief aim is of course to restore the serum protein, which can usually be accomplished by employing the ordinary adequate diet, though oftentimes considerable coaxing and catering to whims will be required in persuading the patient to partake of a diet with normal protein content. Laycock (1944) stressed liver, meat, fish and soy bean derivatives in his cases, and found that rice polishings made into a cake with flour and a little baking powder and fried in peanut oil were well taken especially by the children. Blood transfusions do not always quickly accomplish the restoration. Tube feeding (see Index) will turn the trick, but it is a drastic measure. Occasionally there is temptation to limit radically the amount of salt in the diet, but Weech (1936) warns against the measure as it may only additionally disturb the appetite. Laycock's patients fell into two groups in response to treatment. In one there was a rapid uncomplicated recovery; in the other, in which there was generally persistent albuminuria, progress was very slow, there were disappointing relapses and "a tendency to die suddenly and unexpectedly."

SPRUE

(*Nontropical Sprue, Celiac Disease* [*Gee-Herter-Heubner Disease*], *Idiopathic Steatorrhea* [*Gee-Thaysen's Disease*])

In the middle of the eighteenth century, sprue was observed and described by Hillary in the West Indies. Subsequent modern reports, by Manson in China and Van der Burg in Java, both in 1880, started us off with the fixed belief that this is exclusively a tropical disease, and obscured the two important facts that sprue had actually been described as early as 1669, by Ketelaer, occurring among Belgians in their native land, and that in the present day in temperate zones the disease need only be looked for to be found. Likewise, the peculiar wasting disease of children, first described as "the coeliac affection" by Gee in England in 1888, has so many features in common with sprue that it may now also profitably be considered as identical with that malady—Wilder (1944) probably expresses the consensus of students of the subject when he says that celiac disease bears the same relationship to sprue that cretinism does to adult myxedema. However, McKhann *et al.* (1943) are exploring the possibility that some cases of the celiac syndrome may occur in association with gastro-intestinal allergy; it seems to me that it will be rather difficult to

convince many men of the significance of such an association. Farber *et al.* (1943) feel that diagnosis of none of the types of sprue should be considered established until the pancreatic enzyme activity of the duodenal drainage has been measured, since they have found some patients having a clinical picture resembling that of sprue in whom autopsy revealed obstructive changes due to pancreatic fibrosis.

Sprue, which tends to progress in a series of exacerbations, is characterized by a sore and excoriated tongue and buccal mucosa; excessive intestinal fermentation; stools which contain excessive amounts of split fat and soaps and either resemble dirty brown dishwater or are light-colored, very bulky, fetid and sometimes frothy; a very low "flat" blood sugar curve; a reduction in calcium and phosphorus in the serum; and a blood picture, regarding the formed elements, practically identical with that of pernicious anemia. The abdomen is usually distended and tympanitic; in some instances it is flaccid and has a doughy feel with the patient in the reclining position. There is usually very little abdominal pain but frequent complaint of feeling "sore from mouth to anus." Dilatation of the colon has often been noted; the original demonstrations by Snell and Camp (1934), and Mackie *et al.* (1935), of characteristic roentgenologic changes in the small intestine which vary with the severity of the clinical picture and regress under specific therapy, have been confirmed. Except in the terminal stages, diarrhea is not so frequent as it is exhausting. In long-standing cases the victims become very cachectic and die from inanition or intercurrent disease. Excessive crossness and irritability, periodically accompanied by moderate fatty diarrhea and vomiting, may be the thing which primarily brings the very young patient under medical observation (Hanes and McBryde, 1936); the adult victim also manifests evidences of nervous system involvement, such as insomnia, depression, moroseness, irritability—even apparent subacute combined degeneration of the cord has been occasionally observed (Weir and Adams, 1934; Woltman and Heck, 1937).

The typical anemia of sprue is at first hypochromic and later assumes the hyperchromic-macrocytic type characteristic of pernicious anemia—in adults, that is; that this shift in type does not usually occur in younger individuals is considered to be due to the fact that the bone marrow of children rarely reacts in a hyperchromic-macrocytic fashion, though in adults this form of reaction results from diverse injuries. Rarefaction of bone (osteoporosis) and tetany are characteristics of the disease at all ages, but stunting of growth, infantilism, fractures and bone deformities are seen more frequently in those patients whose malady began as "celiac disease" in infancy; bone pain is more often encountered in young patients also—these differences are likely due to the greater lability and vulnerability of the bone-forming mechanism in youth. Skin disturbances of various sorts are of frequent occurrence in sprue, and the abnormal pigmentation sometimes seen may closely resemble that of pellagra, perhaps even suggest Addison's disease. The van den Bergh (indirect) reaction is not increased in sprue as it is in pernicious anemia, and achlorhydria occurs no more often perhaps than in otherwise normal individuals.

It is currently the accepted opinion that the symptoms of sprue result from a functional disturbance of the small intestine which interferes with absorption; Bennett and Hardwick (1940) refer to the state of the gut as "chronic jejuno-ileal insufficiency." No satisfactory explanation for the appearance of this functional disability has been offered, but Vedder's (1940) tentative explanation of the symptoms may be summarized as follows: interference with

fat absorption causes the steatorrhea and later the diarrhea; later the absorption of glucose is impaired and its resulting fermentation gives rise to the distention and frothiness of the stool; diarrhea diminishes absorption of calcium and iron and of vitamins; the diminished absorption of vitamins sets up a vicious circle through aggravating the intestinal symptoms and causing still further lack of absorption. Stannus (1942), in a thoughtful review of the subject, presents the hypothesis that the primary failure in sprue is one of phosphorylation due to defective enzymic action, the enzymes involved probably having as the active part of the molecule coenzymes embodying some members of the vitamin B_2 complex.

Possibly infestation with intestinal parasites, and other debilitating circumstances, predispose to the malady in the tropics.

THERAPY

Liver Extract.—The use of liver in sprue goes back a good many years; Castellani says that it is an old native remedy in Ceylon. Manson and many of his distinguished successors had been employing liver soup for more than thirty years before recent reiteration of the many similarities of sprue and pernicious anemia freshly introduced liver therapy in its more effective forms. This new use of liver has followed the customary methods of employment in pernicious anemia (see Index for methods), but not always with entire satisfaction until Rhoads and Miller (1934) pointed out that in sprue each case apparently has its own threshold requirement for liver substance, which must be exceeded before a remission can be established. In many instances—either because this threshold is exceedingly high, or through defective absorption—large amounts of liver by mouth are ineffective and even intramuscular injection of liver extract is unavailing; liver extract by vein, however, is life-saving in these cases. Under this treatment, diarrhea ceases (Miller and Rhoads, in 1936, were the first to demonstrate roentgenologically the return of normal functional activity of the small intestine), all the other symptoms disappear and the patient rapidly takes on weight and returns to a completely normal status. It is nearly always necessary, however, to use larger amounts of liver extract than are required in pernicious anemia. The amount of liver extract required to maintain the patient in good health must be individually determined in each case. The belief is widely held that in sprue the crude parenteral liver extracts are superior to the more concentrated preparations; while granting that this may be so, Barker (1943) says that he has seen good results in many patients treated with the concentrated extract and he therefore advocates a thorough trial with such preparations before resorting to the cruder extracts which are more difficult to administer and may cause the patient considerable discomfort. Impending remission is in some instances indicated by beginning changes in the blood picture, but in other patients gastro-intestinal disturbances precede all other signs.

Rodriguez-Molina (1943), reviewing ten years' experience of the liver therapy of sprue in Puerto Rico, says that where the average life duration of the sprue patient was estimated at two years in former times it is now felt that the life expectancy of the patient who is receiving adequate treatment is that of the average person for the same age group, except that for individuals nearing fifty years of age the outlook is still not very favorable. Hanes (1942) has emphasized the fact that now and then a patient is encountered who, though fulfilling the most stringent diagnostic requirements of the sprue syndrome.

nevertheless responds poorly or not at all to therapy. He cites 4 such instances in 60 cases studied in the Duke Hospital Clinic; of the three patients who died, two were examined post mortem without finding an adequate explanation for the fatal outcome.

Nicotinic Acid and Riboflavin.—In 1940, Manson-Bahr used these two agents in a few cases of sprue and found the effects upon the tongue and upon cheilosis as good as those obtained in pellagra. He was therefore led to apply this form of therapy to sprue in general, reporting, in 1941, that in the 24 severe cases of tropical sprue in which the treatment was used (300 mg. of nicotinic acid daily with the addition of 3 mg. of riboflavin if there was an associated cheilosis) the results were highly satisfactory. This is difficult to understand for Bing and Broager (1938), treating 2 patients with nicotinic acid, markedly altered the quantity and consistency of the feces but did not affect the other symptoms; Rhoads (1939) also found nicotinic acid without effect in sprue. Obviously more work is needed in this field. Vedder's (1942) studies in rats are very interesting since they made it appear probable to him that the erythrocyte-maturing factor in liver which relieves the anemia of sprue has no effect in controlling the intestinal symptoms, the latter being regulated by the nicotinic acid in the liver extract.

Diet.—Numerous dietary regimens have had their day in sprue and even now that we are treating cases "specifically" with liver extract, diet is still considered very important. A few patients, once they have recovered under liver therapy, can maintain their health by proper dieting alone, but even if liver extract must be more or less continuously employed a rigid diet must nevertheless be adhered to. The successful diet is one essentially high in protein, with stress upon the taking of large quantities of rare red meats, and in monosaccharides, but low in fat, starches and other polysaccharides. Barker (1943), at the Johns Hopkins Hospital, uses the diet shown opposite in all patients unless the severity of their condition makes it impracticable, in which case they are given nothing but ground meat, bananas and skimmed milk until they can partake of the more liberal diet. Barker finds it often valuable to add dried brewers' yeast or rice polishings to the diet as sources of the vitamin B complex. When fresh milk is not available, dried milk powder has been used satisfactorily.

Adjustment of Therapy for Celiac Disease.—In youngsters with celiac disease, May *et al.* (1942) inject 2 cc. of crude liver extract (Lilly) one day and 4 cc. of parenteral vitamin B complex (Lederle) the next day, the injections being given intramuscularly into the buttocks. These injections are continued for three weeks or until definite clinical improvement is observed; then oral vitamin B complex (Lederle) is given, at least one teaspoonful four times daily, until all the features of the celiac disease syndrome have disappeared. Recently these observers have felt that powdered oral liver extract might be given along with the oral vitamin B complex. In the beginning they use a diet composed of the simple foods well tolerated by these patients (skimmed milk, bananas, curds and scraped beef) and liberalize this diet according to the improvement of the patient. Supplementary administration of vitamins A, B and C is made in about twice the amounts usually employed to meet the accepted daily requirements.

Vitamin K.—Very interestingly, there have been reported several cases in which there has developed a bleeding tendency correctable by administration of vitamin K (see Vitamin K Deficiency). Kark *et al.* (1940) are of the opinion

that hypoprothrombinemia of this sort appears only after long restriction of fatty foods; the obvious thing therefore is to supplement these diets with one of the vitamin K preparations.

Iron.—Observers have pointed out the necessity of adding iron to the regimen when the anemia is microcytic throughout or is converted from macrocytic to microcytic by liver therapy.

Calcium, Vitamin D, Parathyroid Extract.—Whatever may be the cause of the calcium deficiency of the blood in specific instances—whether there is

Breakfast

Toast, one thin slice
Fresh fruit, large serving
Eggs, 2 prepared in any manner desired
Skimmed milk, at least one large glass (this may be heated and used in place of cream for coffee or may be made into cocoa)

Lunch

Meat, large serving (⅓ pound at least)
Vegetables, 2, or one vegetable and salad
Skimmed milk puddings, gelatin, ice cream or fresh fruit
Crackers (2 only) with cheese
Skimmed milk, one glass

Dinner

Fruit cocktail or tomato juice
Beef broth or any cream soup (make cream soups with skimmed milk instead of cream and omit butter)
Meat, large serving (⅓ pound at least)
Vegetables, 2 at least
Desserts, as for lunch
Skimmed milk, one glass

Eggnogs, skimmed milk or fresh fruit may be eaten between meals.

The diet should consist largely of protein:
Meat: Meat should always be lean and rare
Beef, lean, either roast or steak
Lamb, lean, either roast or chops
Ham, lean
Liver, tongue, heart, kidney or sweetbreads
Fish, any fresh fish
Chicken
Lobster, crab or oysters
Milk and milk products: skimmed milk, buttermilk and American and cottage cheese
Eggs: prepared in any manner desired

All fatty foods should be avoided: butter, cream, lard, olive oil and all oil salad dressing, avocado pears, pie, pastry and all foods fried in fat.

All starchy foods should be avoided: potatoes, beans, corn, bread, cereals, cake and candy
(Barker, 1943.)

actual faulty absorption or only excessive loss through the utilization of much calcium to form soaps with the fatty acids in the intestine—the necessity to attempt to supplement the supply is oftentimes quite apparent; indeed, in the series of patients studied by Bassett *et al.* (1939) prolonged liver therapy failed to cause improvement in the absorption of calcium, phosphorus, nitrogen, or fatty acids; moderately high levels of calcium intake did not consistently produce a positive balance in the blood, but when vitamin D was used in addition calcium absorption was obtained. The methods of administering calcium are

under Tetany, vitamin D under Rickets—of the latter preparations viosterol is to be preferred since the fish oils will be poorly absorbed. Intensive ultraviolet light therapy is valuable also. Parathyroid extract should be used very warily since it increases blood calcium only by depleting the bones; Vaughan (1935) especially warned against it in cases in which there is evident bony involvement. It is of interest to note that Batavia powder, the ancient "Peter Sys's Cure" extensively used in Singapore in the old days and still somewhat employed in the East generally, is a proprietary preparation of lime, principally ground cuttle fish bone, I believe.

PERNICIOUS ANEMIA

(See the Section on *Anemias*)

TETANY

The syndrome to which this name is given is characterized principally by carpopedal spasm, *i.e.*, a tonic spasm in which the hands assume the so-called "obstetrical position" with the fingers and thumb approximated and with contracture at the wrist; the arms are often held against the chest and if the lower extremities are involved there is flexion at the knee joint with the feet in the position of equinovarus. There are also generalized convulsions which start in the eye and face muscles and involve the whole body, with consciousness returning as soon as relaxation takes place. Laryngospasm, giving rise to a peculiar crowing sound, is a characteristic symptom; edema of the dorsal surfaces of the hands and feet is sometimes seen. When the arm above the elbow is constricted in an individual with tetany, the hand assumes the accoucheur position (Trousseau). Tapping the cheek over the facial nerve causes rapid contractions throughout its distribution (Chvostek). Use of the galvanic current elicits signs of hyperexcitability of the peripheral nerves (Erb).

By far the most frequently seen of the tetanies is that so often associated with rickets in young children, a type most likely due to decreased absorption of calcium in the absence of sufficient vitamin D. The tetany of sprue is probably also a result of failure of calcium absorption. Frank tetany during pregnancy and lactation occurs but is rare, though tetanoid manifestations such as irritability, painful cramps in the legs, insomnia, transient paresthesias and edemas are of common occurrence. This type is of course easily assumed to be due to loss of calcium, first to the fetus and then in the milk, but it is possible at least that pregnancy and lactation are merely the factors that uncover a latent tendency to parathyroid deficiency. True postoperative tetany is not often seen nowadays but its occurrence is not reckoned a mark of poor surgery since the parathyroid glands are often eccentrically located and also apparently succumb easily at times though not considerably disturbed. In conditions of persistent vomiting and when too much alkali has either been ingested or injected, there occurs a tetany associated with the state of alkalosis. Another sort of alkalotic tetany is that resulting from great loss of carbon dioxide

through abnormally rapid breathing, as occasionally seen in hysterical or otherwise psychically ill persons; Ellsworth and Sherman (1936) have seen an instance of hyperventilation tetany during an asthmatic attack. A type of "idiopathic" tetany in adults is recognized—a group of cases in which none of the above etiologic associations seems to apply; however, this group is probably even much smaller than is commonly believed. Leopold and Jonas (1932) think that a critical analysis would show that most of the cases can really be classified with the infantile type due to vitamin D deficiency. It is further worthy of note, perhaps, that among the small number having no discernible cause other than a spontaneous parathyroid deficiency (comparable to the thyroid deficiency in true myxedema), diarrhea is often present though without the other symptoms of a fully developed case of sprue. Unquestionably tetany appears transiently at times at the height of serious toxic attacks, such as acute poisoning or a febrile state.

Furthermore, the statement, formerly frequently made, that tetany does not occur in the newborn (*i.e.*, under two months of age) has had to be revised, for since 1931 such cases have been increasingly reported, some authors seeing several cases in a year's practice. Kendig (1942) refers to 27 cases in the literature and includes 4 of his own. It seems likely that tetany in the newborn is due in most instances to a temporary hypofunction of the parathyroid glands, but Zahorsky (1937) thinks that some of these cases may be alkalotic (see below) due to prelacteal feeding of alkaline mixtures. In McGavran's (1932) case the condition had undoubtedly developed *in utero* for the baby was born with every one of the symptoms of tetany and responded dramatically to the therapeutic test; he feels that many cases of so-called "birth trauma" might well have been diagnosed tetany and treated as such. McCarrison has described a form of tetany in adult natives of the Himalayas, in association with goiter; it is probably the dietetic, infantile type, for upon removing to a different locality spontaneous recovery occurs.

In all of the above types of tetany there is a disturbance in calcium metabolism, with decrease in blood calcium during the period of active symptoms and rise in the same as improvement takes place; in all, that is, except the gastric, bicarbonate and hyperpneic forms, in which there is a state of alkalosis but normal blood calcium. To explain this discrepancy, we assume that the important matter in tetany is not how much calcium there is in the blood stream but how much of it is ionized; a shift to the alkaline side is thought to decrease ionization. This may be a correct explanation, as it is certainly a serviceable one, but the fact is that there has not yet been devised a method for determining the amount of calcium ion in the blood, and the assumption that it is equivalent to the amount of diffusible calcium can be justified only upon the score of convenience. Since calcium deficiency and the full symptomatology of tetany are not necessarily parallel phenomena, and because chronic cases tend to become less severe (latent), it has become recognized that there are undoubtedly other factors of importance in etiology—certainly the relationship between calcium, phosphorus and carbohydrate metabolism is a close one. Several groups of investigators have shown that the calcium variation can only be properly interpreted in conjunction not only with the inorganic phosphorus but with the serum protein also. Tetany does not occur characteristically in chronic nephritis, though there is often a distinct reduction in serum calcium; however, McCullagh and Ryan (1939) have recently reported an interesting case of tetany in an adult in association with renal insufficiency.

Miller (1944) has reported a case of tetany which he felt was caused by a low plasma magnesium content occurring in a child of six years who also had osteochondrosis of the capital epiphysis of the femur (Legg-Perthes disease).

The first empiric use of calcium in tetany was probably that of Walter Harris, of London, who in 1689 "accomplished cure with no other medicines than a few ounces of crabs' eyes mixed with crystals of tartar." Shelling (1932) states that among Negroes of the eastern shore of Maryland the use of shells in the treatment of this disease has been handed down in some instances as a family secret through several generations. The first rational employment of calcium as an anticonvulsant was that of the Italian, Sabbatini, in 1901.

THERAPY

Calcium Salts by Mouth.—There has been an unfortunate lack of understanding of the proper method of administering calcium by mouth which, if it is now corrected, should greatly improve the results obtainable, I should think. Theoretically, calcium lactate is the ideal salt because it does not change the reaction of the tissues, but it has given very poor results as ordinarily used, *i.e.*, taken in tablet form or stirred up in milk. Therefore calcium chloride, which is very irritating to the stomach and tends to cause acidosis, is most frequently used because its very acidity promotes its absorption. But often calcium chloride, if given in tablet form or in milk, also fails to raise the calcium level of the blood and check the symptoms. It seems the trouble lies in the fact that we have all overlooked an important piece of work of Roe and Kahn, in 1927, in which they showed that a 91 per cent rise in blood calcium could be obtained in the human by the administration of 75 grains (5 Gm.) of calcium lactate dissolved in water as against only a 28 per cent rise when the same dose was given hourly for eleven hours (a total of 55 Gm.) dissolved in milk. Roe (1938), in recently calling attention to this earlier work, attributes the fine results obtained with calcium lactate to the fact that the salt was not given mixed with a food which would cause an increase in the alkalinity of the intestinal tract and thus lessen calcium absorption. Wilson (1938), however, reports a case in which both calcium gluconate and calcium lactate failed to cause relief when given in milk or tablet form but in which calcium lactate dissolved in water and taken orally invariably gave as quick relief as a calcium salt given intravenously; he attributes this action to the fact that the salt was dissolved in water for oral use and not that it was not given with food.

The lesson to draw from the above, it seems to me, is that we have been giving calcium salts improperly by mouth and that for best effects they should be given dissolved in considerable water; and furthermore, that when so used calcium lactate is likely to give as good account of itself as calcium chloride or calcium gluconate.

Adult dosage of calcium salts is usually 90 grains (6 Gm.) or more distributed throughout the day. Sometimes ammonium chloride is also given to increase the ionization of calcium, 75 grains (5 Gm.) or more daily in divided doses. Dilute U.S.P. hydrochloric acid may be used in the same way, a teaspoonful (5 cc.), well diluted in water or milk, four to six times daily. It has been stated that the use of half as much lactose as calcium lactate per dose promotes the absorption of the latter, but there is not apparently much confirmation of this in clinical experience; McCullagh's (1932) is the latest report I have seen.

McGavran (1932) handled his patient, born with tetany, as follows: "cal-

cium chloride, 7 grains (0.45 Gm.) every hour; viosterol, 3 drops every two hours; phenobarbital, 1/12 grain (0.005 Gm.) every four hours. Forced feedings, 1 ounce of breast milk, every hour, were administered with a medicine dropper. It took forty-five minutes out of every hour to get the ounce down. In twenty-four hours the calcium chloride was stopped as it produced vomiting. The phenobarbital was stopped in forty-eight hours. In ten days the baby became a simple feeding problem and has developed so far into a perfectly normal healthy twelve months old baby."

Calcium Salts by Injection.—Under urgent circumstances such as severe convulsions and glottic spasm, 5 to 20 cc. of a 5 per cent solution of calcium chloride, or 10 per cent calcium gluconate, may be given intravenously; for the precautions to be observed in the intravenous administration of calcium salts, see Lead Poisoning. Subsequently, 10 cc. of the gluconate solution can be given intramuscularly once or twice daily. Almost as large doses are used in infants as in adults. The local precipitation of calcium salts following the intramuscular injection of calcium gluconate in the treatment of tetany of the newborn has been reported several times. Shannon (1938) has reported 2 cases in which calcium salts were not only precipitated at the sites of injection but also at remote points in the body; reabsorption eventually occurred in both instances without known permanent damage.

Viosterol and Fish Oils.—These vitamin D preparations are used routinely in all infantile cases; there are reports of their satisfactory employment for the promotion of calcium absorption in various other forms of tetany also. (See Rickets for methods of using these agents.) Very interestingly, Sevringhaus and St. John (1943) have successfully replaced dihydrotachysterol (see below) with high vitamin D therapy in six women with permanent and severe hypoparathyroid tetany, the duration of the treatment being two years or longer in four of the cases. The doses varied from 150,000 to 400,000 U.S.P. units daily; calcium salts were also given by mouth. Dietary restrictions which had previously been considered necessary were withdrawn and the patients were allowed to take as much meat, eggs and milk as desired in spite of the higher phosphorus intake involved.

Dihydrotachysterol (A.T. 10).—This agent, introduced by Holtz (1933), in Germany, is making a good name for itself nowadays. It is a chemical substance derived from a fraction of irradiated ergosterol, hence closely related to vitamin D. The study of Albright *et al.* (1938) showed that, like vitamin D, it increases calcium absorption from the gut and phosphorus excretion in the urine. In America it has been used principally in postoperative parathyroid tetany (Margolis and Krause, 1939; Hurxthal and Claiborne, 1939; Ryan, 1940), but Franco (1940) used it very successfully in a case of chronic idiopathic tetany of ten years' standing in which all other types of therapy were inadequate for control, and Bloxsom (1940) found it ideal for treatment of a case of tetany of the newborn.

Dihydrotachysterol is marketed in 0.5 per cent solution in sesame oil and is stable, but unfortunately it is still quite expensive; it is given by mouth. In severe cases of postoperative tetany some men have used as much as 10 to 20 cc. daily for a few days and then sharply reduced the dosage, but Ryan (1940) probably expressed what by now is the consensus in saying that in most instances even of severe tetany the dose should not exceed 2 cc. daily; subsequently the maintenance dosage must be worked out in each case; some individuals require from 0.5 cc. upwards daily, others do well on very small dosage

only once or twice weekly. In his case of tetany of the newborn, Bloxsom was obliged to use 15 drops three times daily in order to initiate improvement. If calcium is given by mouth in addition, dihydrotachysterol dosage can be much reduced.

This is a dangerous drug because it can easily cause hypercalcemia (see symptoms under Parathyroid Extract, below) and should not be used in the present state of our knowledge unless frequent observations can be made of the blood calcium and phosphorus levels.

Parathyroid Extract.—Though probably soon to be more or less completely replaced by dihydrotachysterol (see above), this drug has until recently been the one of choice in resistant cases of postoperative tetany. It is always supplemented by large doses of calcium by mouth. In severe cases with serum calcium values as low as 5 mg. per 100 cc. (the normal is 10 to 11 mg.), from 40 to 60 units may be given intravenously and half the dose subcutaneously or intramuscularly four to six hours later. Probably in most cases, 30 to 40 units daily will maintain the serum calcium at normal after this level has been reached, but the action varies markedly in different individuals, and in many cases an immunity develops after a few weeks so that even much increased doses are ineffective in influencing the blood calcium or phosphorus. Shelling and Goodman (1934) believed that in such instances we are not dealing with resistance to parathyroid but rather with factors conducive to increase in the intake of phosphorus; upon the basis of very satisfactory experience in 2 cases, they recommended the trial of low phosphorus diets in parathyroid tetany. Boothby and Davis (1936) also favored the use of such a diet, plus calcium salts in large doses with adequate amounts of vitamin D, and only the occasional administration of parathyroid extract. In infantile tetany the response to parathyroid has been extremely variable and perhaps upon the whole unsatisfactory. In maternal cases, small doses of the extract plus calcium salts have been used satisfactorily. In 2 of Snell's (1932) 4 cases of sprue tetany the drug was effective but it failed in the other 2; indeed, as he indicated, the fault here is not in parathyroid insufficiency and therefore if the extract is to be used it must be fortified with full doses of calcium.

Parathyroid extract is a powerful agent and it is extremely important to guard against overdosage. Perhaps the earliest symptom is vomiting, so that when this occurs in an individual taking the drug an immediate check upon the blood calcium should be made. Later there is increasing listlessness, perhaps high fever, and finally coma. Other than immediate cessation of the injections, the treatment rests upon a very insecure foundation. Lowenburg and Ginsburg (1932) employed venoclysis to aid excretion of calcium and possibly also of parathyroid extract and to dilute the blood, which, at least in animals, becomes very viscid and markedly decreased in volume. The administration of calcium at the same time in order to prevent decalcification seems rational.

The Treatment of Alkalotic Cases.—In these cases of course the principal indication is to overcome alkalosis, which is usually easily accomplished if overdosage of alkalis has been at fault. Where loss of chlorides through vomiting obtains, physiologic solution of sodium chloride must be given in large quantities by all the usual channels. Ammonium chloride may be given by mouth, or intravenously in amounts of 300 to 500 cc. of 0.82 per cent solution, first testing the solution, as recommended by Cantarow, to see whether it causes hemolysis. In the hyperpneic cases there is often difficulty in controlling the causative factor, namely, the hysterical attacks of rapid breathing in

psychically disturbed individuals. In one such patient, when an attack had been precipitated by excitement, Meakins (1930) proved that alkalosis was the causative factor by producing instantaneous remission when the patient was caused to inhale a mixture of 5 per cent carbon dioxide and 95 per cent oxygen. The paper-bag method (see Hiccup) might be expected to appeal to such patients.

Treatment of Tetany from Magnesium Deficiency.—In Miller's case, previously referred to, the patient, who was six years of age, was given 5 grains (0.3 Gm.) of magnesium sulfate by mouth three times daily; striking symptomatic results were said to have been obtained.

XEROPHTHALMIA

This entity (vitamin A deficiency) is characterized principally by night-blindness (hemeralopia), changes in the skin, and certain corneal symptoms, to which last is applied the term keratomalacia. In the lands where the disease is endemic the victims are principally children or young adults. Insidiously progressive difficulty in seeing well after nightfall is usually the first evidence of the disease; in rats deprived of vitamin A in the diet, the disturbance has been shown to be due to failure of regeneration of visual purple in the retina. The later gross signs and symptoms are redness of the eyes, lacrimation, photophobia, pain in the eyes, wrinkling of the conjunctiva, and failure of vision associated with yellowish-white areas on the cornea, which spread until the entire cornea becomes uniformly hazy and insensitive and finally necrotic and ulcerated. A rather large variety of skin abnormalities has been found associated with xerophthalmia, but most notably excessive dryness and follicular hyperkeratosis. Vaginitis has been described as due to vitamin A deficiency and also keratinization of the bronchial epithelium, the latter giving rise to atelectasis and bronchiectasis and complicating pneumonia.

Night-blindness and its response to liver therapy was recorded in the Egyptian Papyrus Ebers, a thousand years before Hippocrates. But keratomalacia as a part of the syndrome was first mentioned by Brown, in England, in 1827. Block demonstrated vitamin A deficiency as causative, in Denmark, in 1921. Xerophthalmia is common in China, Japan, India, Ceylon, Netherlands Indies and the British Solomon Islands, certain portions of Russia and of "native" Africa, Yucatan and British Guinea. During War I it became a serious problem in Germany and Austria and was also widespread in Denmark, the incidence in this latter country being due to the high price commanded by butter and the consequent substitution of A-deficient oleomargarine and lard in the Danish dietary. The disease appeared in England during the economic depression preceding War II and at present must surely be holding sway in the plundered countries on the Continent, though of course we will have no statistical evidence of the fact until some time after liberation of these peoples has been completed. In the United States the full syndrome as described above is not seen since the worst diet likely to be taken by our most poverty-stricken groups apparently contains enough vitamin A to be partially protective. However, in recent years surveys based upon studies with the dark adaptation photometer indicate the likelihood that lower income groups are

often obtaining suboptimal amounts of the vitamin, though it must be admitted that there is not complete agreement regarding the validity of such photometric tests. But Jeghers (1937) clearly demonstrated that the early stages of xerophthalmia—night-blindness, photophobia, dry skin, dry conjunctivae, blepharitis and follicular hyperkeratosis—need only be looked for to be found since he observed one or more of these symptoms, which responded to the therapeutic test of vitamin A administration, in 12 per cent of a group of 162 medical students. In these students the skipping of meals and poor choice of foods, rather than absolute poverty, were chiefly at fault, but Spies (1939), employing the same clinical criteria, found early xerophthalmia with considerable frequency in his nutrition clinic in Birmingham, Alabama, where poverty and the unavailability of suitable foods are the determining factors. Likewise in New York, Lehman and Rapaport (1940) found early xerophthalmia among the children of the poor. Decidedly then, vitamin A deficiency does exist in the United States among the chronically undernourished classes; it is well to bear in mind also that the following factors may contribute to its appearance in anyone: rapid growth, fever, infection (especially chronic infection), pregnancy, increased basal metabolic rate, gastro-intestinal and hepatic disturbances, elimination and other types of therapeutic dieting unless closely controlled, "slimming," psychoneurotic tendencies with peculiar dietary habits. Carotene absorption is said to be prevented by liquid petrolatum but I do not know of any cases of xerophthalmia as yet which were definitely ascribable to the use of this oil as a laxative.

Regarding vitamin A deficiency and susceptibility to respiratory and other infectious processes, one can only say that there is no body of evidence in existence which reliably shows that such a relationship exists. Therefore, given an infant or adult on a balanced nutritious diet, nothing is to be gained in the way of protecting him from colds or other communicable diseases by adding additional vitamin A to the diet.

THERAPY

Cure is very simply and easily achieved if the patient can be placed on a diet containing sufficient vitamin A or its precursor, carotene. The eye symptoms usually abate in a few days and are completely gone in a few weeks, but the skin symptoms often require several months to disappear. The animal foods richest in vitamin A are milk, cream, cheese, butter, eggs, fish roe and liver. Vegetables and fruits contain carotene and must be employed in large amounts in order to make good quantities of the vitamin available; the best of these are spinach, carrots, squash, sweet potatoes, lettuce (the outer green leaves are best), peas, peppers, tomatoes, apricots and prunes. Light cooking of any of these fruits or vegetables is not harmful, indeed it may even make their carotinoids more readily available, but stewing for many hours in an open vessel causes considerable loss due to oxidation (Clausen, 1943). Cod and the other fish liver oils are also excellent, but viosterol and ultraviolet irradiation are worthless, since it is not vitamin D that the patient is lacking. Vitamin A is not yet clinically obtainable in pure form, but carotene has been made available. The Council-accepted (1944) products for clinical use are: carotene in cotton seed oil; the same with vitamin D added; and carotene with vitamin D in cod liver oil. Exact dosage has not yet been developed for these preparations; they are at present administered in about the same dose as cod liver oil of equivalent potency (see Rickets). Youmans (1939) has seen a few cases in

which there was a brief exacerbation of the symptoms when use of these highly fortified oils was begun. Kirwan *et al.* (1943), in Calcutta, have introduced vitamin A parenterally, but preparations for this type of administration are not available to my knowledge in the United States.

Josephs (1944) has reported a case of severe hypervitaminosis A occurring in a boy of three years who had received about 240,000 U.S.P. units of vitamin A daily since he was about three months of age. The condition was characterized by hepatomegaly, splenomegaly, hypoplastic anemia, leukopenia, increased serum vitamin A, increased serum lipids, advanced skeletal development, clubbing of the fingers, and sparse, coarse hair; it was accompanied with an abnormal appetite for halibut liver oil, the source of the vitamin. Most of the symptoms cleared promptly when the excess vitamin A was removed from the diet.

VITAMIN K DEFICIENCY

(*Hypoprothrombinemia*)

Numerous studies in recent years, principally in Denmark and the United States, have clearly revealed the fact that there are circumstances under which the supply of prothrombin in the body is below the amount necessary to insure clotting of the blood when a break occurs anywhere in the vascular system. It has furthermore been determined that these instances of hypoprothrombinemia are principally the result of deficiency in vitamin K, a factor essential to the production in the liver of the substance, prothrombin, without which clotting of the blood does not occur. Mammals including man obtain this vitamin normally from two sources. First, it is a dietary constituent, being present in particularly large amounts in such plants as alfalfa and spinach, and in appreciable amounts in such green vegetables as cabbage, cauliflower, kale, carrot tops, etc. Second, it is produced by bacterial action in the lower bowel even on a diet devoid of the vitamin. It is now also available for therapeutic use in the form of relatively crude extracts obtained from alfalfa and from putrefying fish meal and a number of other substances. Recently, also, several synthetic substances with vitamin K activity have become available; for the one of these which is apparently most active—2-methyl-1, 4-naphthoquinone—the Council on Pharmacy and Chemistry has adopted the name "menadione." Prothrombin deficiencies of clinical significance are seen under the following circumstances:

Liver Disturbances.—The liver is of great importance in the maintenance of a normal prothrombin level for two reasons: first, it is the site of the formation of prothrombin, a synthesis in which vitamin K, absorbed from the gastrointestinal tract, plays a vital part; and second, vitamin K is a fat-soluble substance which is poorly absorbed if the liver does not pour sufficient bile into the intestine. The bleeding tendency both in obstructive jaundice and in cases of biliary fistula is now recognized to be due to hypoprothrombinemia, the absorption of vitamin K being reduced in the first instance by the reduction in the amount of bile which reaches the gut, and in the second instance by the diversion of bile from the gut. These matters have been elucidated largely through the observations of Quick at Marquette, Smith and associates at Iowa, and Snell and associates at the Mayo Clinic; the review of

Brinkhous (1940) will lead the interested reader into the early literature. Further than this, it now seems that hypoprothrombinemia can result from liver disease *per se*, that is, without a sufficient depression or diversion of bile to prevent adequate vitamin K absorption—for example, in some instances of infarction, liver abscess, or cirrhosis. It is assumed that the bleeding tendency in these instances is due to the inability of the liver to form prothrombin even though ample vitamin K is being absorbed from the gut.

Gastro-intestinal Disturbances.—The Mayo group have studied a series of patients with intestinal lesions of a diverse nature: intestinal obstruction, postoperative gastric retention, sprue, chronic ulcerative colitis, internal and external fistulae. In some of these cases hypoprothrombinemia and its consequent bleeding tendency were found, the fault lying apparently in an insufficient amount of normal intestinal mucosa for adequate absorption of vitamin K, insufficient absorption as a result of fat-poor dieting in the sprue cases, prolonged diarrhea, or long-continued aspiration of duodenal contents. Others have reported similar findings.

Nutritional Deficiencies Other Than Sprue.—Kark and Lozner (1939) reported 4 patients each having a dietary deficiency disease apparently unassociated with any liver disturbance; in each there was hypoprothrombinemia. Scurvy was diagnosed in 3 of these cases and pellagra with subclinical scurvy in the other. It will be interesting to see whether other observers can find such cases because it is difficult to understand how the mere taking of a diet deficient in vitamin K could reduce the plasma prothrombin since the bacteria in the lower bowel are able to form the vitamin from food residues entirely devoid of it. However, Warner and Owen (1942) found that patients in pernicious anemia relapse frequently manifest hypoprothrombinemia which does not respond to vitamin K administration but disappears when liver therapy is instituted.

Hemorrhagic Disease of the Newborn.—It is now established that the prothrombin level of the blood of newborn infants often drops rather precipitously during the first days of life and is then restored spontaneously. The hemorrhagic episodes occasionally seen during the first few days are generally looked upon as due to this hypoprothrombinemia, which Waddell and Guerry (1939) were the first, I believe, to show could be effectively both treated and prevented by the administration of vitamin K. Quick and Grossman (1939) offered as explanation of this type of hypoprothrombinemia the hypothesis that very little storage of prothrombin or of vitamin K takes place in the fetus, that exhaustion of this small amount quickly occurs after birth, and that the build-up toward the normal and safe quantity only begins with the establishment in the intestine of bacteria which synthesize the vitamin, which, in the presence of bile, is then absorbed. Salomonsen and Nygaard (1939) are said to have shown (I have not seen their publication) that hypoprothrombinemia of the newborn can be almost completely prevented if small quantities of cow's milk or breast milk are given to newborn children to form "a nourishing substratum for those microbes which very rapidly enter per os and per annum." In Sweden, Lehmann (1944) has made a large scale application of vitamin K prophylaxis covering 13,250 newborn infants who were given the vitamin and 17,740 untreated controls. He found that about 1.6 full term infants per 1000 treated have been saved by the treatment, concluding that if in Sweden, with 100,000 full term infants born annually, there were a general employment of prophylactic vitamin K, 160 infants might be saved yearly. Upon the other hand, in the United States, Sanford *et al.* (1942) studied 1693

infants over a period of two years, employing vitamin K in 711 of them, reporting that though the plasma prothrombin level of the blood of the treated infants was raised to well above normal through the administration of the vitamin, the frequency of hemorrhagic manifestations was just the same in the treated as in the untreated group. In discussing this latter report, Quick pointed out the likelihood that in some instances the injury to large vessels might be so extensive that the hemostatic defenses alone would be unable to cope with the bleeding. However, Parks and Sweet (1942), also in the United States, found that the agent had no effect in reducing the incidence of neonatal hemorrhage in a series of 1151 infants with 1594 infants as untreated controls. It begins to appear that in some instances of hemorrhagic disease of the newborn, hypoprothrombinemia is not responsible for the bleeding. Scobbie (1942) reports five cases in which she says the prothrombin levels were relatively high. Allibone (1943) has accounted for one case on the basis of congenital fibrinopenia and another on the basis of transient afibrinogenia, while Baar (1941) writes of a qualitative platelet defect.

Idiopathic Hypoprothrombinemia.—It is difficult to know just where to place such cases as the following. Rhoads and Fitz-Hugh (1941) describe an eighteen-year old patient with a hemorrhagic diathesis extending throughout most of his life, the defect appearing to be due to an "idiopathic" hypoprothrombinemia coupled with an abnormality of the fibrinogen. Giordano (1943) reported a case which appeared familial since other members of the family also had low prothrombin levels. Quick (1944) has found a consistent prothrombin level of 45 per cent in a medical student who is normal in all other respects.

THERAPY

Various vitamin K preparations have been prepared from alfalfa, cereals, fish meal, and the like, and all have been shown to have value in effecting a quick rise in plasma prothrombin; however, since the synthetic substance, Council-accepted as menadione (2-methyl, 4-naphthoquinone), is more potent than any of these or than any of the other closely allied naphthoquinone synthetic substances, it seems to me advisable to confine the present article to a description of the methods of employing menadione only.

Liver Disturbances.—At the Mayo Clinic, according to Butt (1940), patients with jaundice are divided into three groups for routine preoperative handling: (*a*) those in whom the prothrombin time is normal; (*b*) those in whom the prothrombin time is prolonged (*i.e.*, there is some degree of hypoprothrombinemia) but in whom active bleeding has not occurred; and (*c*) those in whom prothrombin time is prolonged and active bleeding occurs. To those with a normal prothrombin time, vitamin K is administered for two to five days before surgical intervention is undertaken; this is simply a prophylactic precaution. In those having a prolonged prothrombin time without bleeding it is often thought advisable to administer the agent through a duodenal tube. In those who are actively bleeding, whole blood transfusion is many times necessary in addition to the administration of the vitamin. Butt makes the point very strongly that despite a rise in plasma prothrombin during the first few postoperative days, the studies must nevertheless be made daily for the first four days and every second day thereafter for eight or ten more days because of the likelihood of a postoperative fall in prothrombin and the beginning of severe bleeding. This postoperative decrease in prothrombin has been remarked by many others, but its cause is not yet known. Cullen *et al.* (1940)

probably find many in agreement with them that anesthetic damage to the liver is responsible; however, Allen and Livingstone's (1941) studies in dogs caused them to conclude that the state does not result from the employment of the usual anesthetics (exclusive of chloroform) but is the result of inadequate preoperative use of the vitamin. Lord (1939), also using dogs, found that trauma to the liver, such as might occur during difficult operations on the biliary tract, may cause a very great decrease in plasma prothrombin.

Patients are not infrequently seen who respond very sluggishly or practically not at all to vitamin K therapy. The natural inference has been that these failures were due to an impairment of the liver's ability to form prothrombin even when supplied with the necessary vitamin. Quick (1940) has said that it seems important now to correlate liver function and the patient's response to vitamin K. In fact, several such studies have been performed but the findings are not entirely in agreement either with each other or with clinical experience. Wilson (1939) found a high degree of correlation between liver function, as revealed by the hippuric acid test, and the plasma prothrombin concentration. This was upon the whole also the experience of Stewart and Rourke (1939), Pohle and Stewart (1940), and Rawls (1941). Smith *et al.* (1939) state rather emphatically that when the liver is severely injured there is a fall of plasma prothrombin which cannot be corrected by the administration of vitamin K; Kaplan *et al.* (1943) report one such case in a newborn infant with massive infarction of the left lobe of the liver. However, Lucia and Aggeler (1941) find that (*a*) there is no significant correlation between the results of the hippuric acid liver function test and the level of plasma prothrombin; and (*b*) plasma prothrombin concentration may be elevated to normal by the administration of vitamin K despite markedly impaired liver function as revealed by the hippuric acid test. Butt *et al.* (1940) also state that a severely damaged liver does not preclude prothrombin formation; they have seen patients who by every known clinical and laboratory test were convicted of hepatic insufficiency and who were nevertheless able to utilize vitamin K and maintain a normal plasma prothrombin level.

Oral Administration.—In average cases 1 or 2 mg. together with 5 or 10 grains (0.3 to 0.6 Gm.) of bile salts seem to suffice to elevate the prothrombin level to normal in twelve to twenty-four or thirty-six hours, according to Butt *et al.* (1940) of the Mayo Clinic. The duration of such action varies with the individual case. Some men have been giving larger doses than the Mayo group; for example, all of Allen and Julian's (1940) patients received at least 8 mg. daily; however, N.N.R. (1944) states the daily dose as 1 to 2 mg. and says that the 2 mg. dose should not be continued for a period exceeding four weeks.

Intramuscular Administration.—N.N.R. (1944) lists ampules containing the drug in 1 and 2 mg. amounts in sesame or corn oils. These ampules have been used very satisfactorily by a number of observers, who find with Andrus and Lord (1940) that in most instances the response to a single 2 mg. injection occurs in about eight hours.

Bile salts do not have to be given when the vitamin is injected intramuscularly.

Intravenous Administration.—Tocantins and Jones (1941) prepare menadione for intravenous use as follows: 10 mg. quantities are sterilized in dark amber ampules and kept in the dark; for use, the content of an ampule is dissolved in 1 cc. of absolute ethyl alcohol and slowly poured into 50 cc. of warm sterile physiologic salt solution in a flask wrapped in black paper. The pro-

thrombin rise often begins within three hours of the intravenous administration of an amount of this solution containing 1 mg. of the active agent. Norcross and McFarland (1940) prepared their solutions by dissolving 10 mg. of the agent in 100 cc. of sterile hot physiologic salt solution and using as soon as sufficiently cool for injection or after storage, protected from light, in a refrigerator for only a short while. These workers find 2 mg. the minimal effective dose.

Bile salts do not have to be given when the vitamin is administered intravenously.

Gastro-intestinal Disturbances.—There are no peculiarities of hypoprothrombinemia due to gastro-intestinal disturbances which require special mention from the standpoint of therapy except that of course in some of the cases absorption of the vitamin may not follow its administration by mouth.

Hemorrhagic Disease of the Newborn.—The most usual method of employing menadione to prevent the "physiologic" hypoprothrombinemia of infants (hoping thus to prevent the occurrence of the occasional case of bleeding) is that employed by Huber and Shrader (1941) in their series of 200 infants: drop 1 mg. of the agent dissolved in oil on the back of the infant's tongue at six and again at thirty hours after birth; Mull *et al.* (1941) like to give 1 mg. at eight-hour intervals for three doses. This oral type of administration will suffice for treatment also in instances in which bleeding is occurring when the infant is first seen. But there are also other methods. For example, there is the percutaneous application of the vitamin in an ointment base, as described by Russell and Page (1941); an amount of the ointment containing 10 mg. of the agent is rubbed thoroughly on the skin of the back during the first and second days of life. Page and Bercovitz (1942) observed considerable cutaneous irritation when using this ointment in adults and therefore abandoned it, but Vollmer *et al.* (1942) have very successfully employed the agent in an ointment base of their own devising. Or the agent may be given intramuscularly in 1- to 2-mg. doses, as in the adult. Hellman and associates (1940) at Johns Hopkins, and a number of other groups since, have found that the most effective method of accomplishing the desired rise of prothrombin in the infant is to administer the vitamin to the mother; usual practice is to give 2 mg. during labor. Very interestingly, Fitzgerald and Webster (1942) have shown that the administration of barbiturates definitely decreases the prothrombin level in the mother and child and that this decrease can be prevented by the administration of menadione during labor; Hardwicke (1944), however, was unable to confirm the depressant effect of the barbiturates.

The studies of Lawson (1941), and Willumsen *et al.* (1941), indicate that intramuscular injections of whole maternal or paternal blood in the usually employed quantities of 10 or more cc. at four- to eight-hour intervals have very little effect in combating the hypoprothrombinemia of the newborn; even intravenous transfusion, a difficult procedure in the infant, is much less effective than vitamin K administration.

ENDOCRINE DISTURBANCES

ENTITIES WHICH SHOULD BE LEFT TO THE SPECIALIST

There is a great stir in the field of endocrine investigation nowadays, with the result that much hullabaloo has been raised to favor the extensive employment of commercially available "hormone preparations" in treatment of the endocrinopathies. The result is that those of us who are brash and immodest enough to write books are being constantly appealed to with the plea to "straighten out" these matters—which usually means these commercial products—for the general practitioner. Sitting in the meetings of the endocrinologists, listening to the conversations of some of my friends who are of that persuasion, studying the literature, rolling things around in my mind, I come to the conclusion that most of the endocrinopathies are still susceptible of satisfactory handling only in consultation with, or entirely by, specialists in that clinical field. These gentlemen do sometimes accomplish quite satisfactory results, but no one is better aware than are they themselves what a prodigious expenditure of time, what an exhibition of diagnostic acumen derived from their special training, and what an amount of frank but cautious and above all expertly calculated therapeutic tinkering is required for them to arrive at such goals as they achieve. The following, in addition to an increasingly large group of entities whose very names ring queerly in the ears of an ordinary medico, are best left alone by the general man, in my opinion: acromegaly, Simmonds' disease (pituitary cachexia), pituitary dwarfism and infantilism, Fröhlich's syndrome (adiposogenital dystrophy), pituitary basophilism, pituitary habitual abortion, pituitary bilobar disorders, pituitary myxedema, sterility (this entity often requires the cooperation of gynecologist and urologist as well), Dercum's disease (adiposis dolorosa), hermaphroditism, cryptorchidism (undescended testes), sexual underdevelopment, virilism, gigantism, Laurence-Moon-Biedl syndrome, hyperparathyroidism, adrenogenital syndrome.

ENDOCRINE THERAPY IN MENSTRUAL DISTURBANCES

(See *Menstrual Disturbances*)

CRETINISM

Cretinism is an affection originating during fetal life or in infancy, characterized by retarded mental and physical development, and due to the absence or more or less complete atrophy of the thyroid gland. Practically nothing is known of the cause of this abnormality. It occurs all over the world but is most prevalent in goitrous regions, though curiously enough it is relatively

rare in North America; however, with regard to this last point, Stoddard's (1933) study indicated that in Wisconsin, and by inference in other Great Lakes regions and in the Pacific Northwest, the state of endemicity of cretinism is probably quite imminent. Among preserved records the first reference to cretinism is that of Paracelsus, in the sixteenth century, though of course the entity must have been prevalent long before that period.

Most patients do not come under observation until they are six to eight months old because failure to develop normally is not often noticed before that age. In typical cases the general appearance is characteristic, regardless of the child's age. The hair is dry, coarse and usually scanty; the face is broad, with a wide flat nose, thick lips, protruding tongue and heavy jaw; the fontanels remain open, the forehead is low, the abdomen is large, and there is often an umbilical hernia; bony growth is delayed, but the hands and feet are large and the toes and fingers short and thick; dentition is delayed, temperature is subnormal, the skin is dry and the tissues have a doughy feel but do not pit upon pressure. Constipation is the rule. Cretinous individuals are undersized physically and very much stunted mentally. Their characteristic response to questioning is a wrinkling grin, and their ultimate mental development is usually into a clownish sort of childishness in which they seem very happy; any type of idiocy, however, may be seen. The state of untreated cretinism is not incompatible with attainment of full years, but most victims of the affection succumb fairly early to one of the infectious diseases.

THERAPY

The response of cretins to the administration of desiccated thyroid substance (*nota bene:* this substance is not an extract, therefore the term "thyroid extract" is not permissible; see also the note regarding differences in brands in Myxedema) is well known to everyone. Osler has written: "Not the magic want of Prospero or the brave kiss of the daughter of Hippocrates ever effected such a change." And truly written, for the change is as rapid as it is remarkable. One needs but to start with a small dose, build it up as tolerance and necessity dictate, and then watch during the brief space required for the conversion of an imbecile into a rational being. Regarding dosage, Kerley writes from his wide experience: "The required thyroid dosage is very readily learned; the child adjusts itself to the amount it requires. We usually begin with about $\frac{1}{4}$ grain twice a day, and then increase as necessary until we get results." In the beginning there is considerable sweating and loss of weight and the previously phlegmatic child becomes hyperactive, irritable and hard to manage; Wilkins (1940) says that these symptoms, which probably indicate only a slight and desirable degree of hyperthyroidism, may be disregarded. The toxic symptoms indicative of overdosage are diarrhea or cramps, vomiting, excessive irritability or twitchings, continued loss of weight, a very rapid pulse rate and fever; when such symptoms occur, Wilkins omits the drug for a few days to a week and then resumes its use with a dose $\frac{1}{2}$ grain (0.03 Gm.) lower than that previously given. This author does not consider the apparent disappearance of all clinical symptoms as an adequate criterion of the adequacy of thyroid therapy, but is guided by the degree to which the "bone age" and "height age" of the patient keep pace with the normal. Unless there is continuous rapid development of the osseous system he likes to increase thyroid dosage if the patient can tolerate it; if the bone age exceeds the normal or passes too far beyond the height age the dose is decreased because when the bone age reaches

that of thirteen or fourteen years epiphysial union begins and growth ceases. It seems rarely to be necessary to exceed a dose of 3 grains (0.2 Gm.).

In 1940, Kerley reported nine individuals, ranging in age from sixteen to forty years, whose development as regards not only height and weight but also mental endowment he considered normal. Unfortunately, however, the prognosis for normal mental attainment is not as good as for physical development. As a result of their study of 29 cretins, Brown *et al.* (1939) said "a small proportion" of them may attain normal mental development. Bruch and McCune (1944), basing their opinion on a statistical examination of the data from the study of 23 patients, say they are persuaded that one must observe caution in predicting the intellectual future of congenitally hypothyroid children, irrespective of both the time at which treatment is first instituted and adequacy of the treatment as judged by physical criteria. In 1936, Kerley last reviewed a case on which he had several times previously reported; a woman of thirty-five who was competently treated from the age of two months but in whose mental development there were such gaps as inability to compose a letter or to attain any appreciation of mathematics; she reads and writes but when engaged at the latter she inserts words which have no meaning in the context; she has worked for many years in the same low-grade employment because unable to take promotion.

Bruch and McCune (1944) warn that whereas intensive treatment is warranted during a trial period, the fact must be kept in mind that overdosage can cause serious disorders of behavior, and that unless such dosage is clearly productive of proportionately improved mental development, the social and emotional problems which it may engender must not be ignored.

MYXEDEMA AND HYPOTHYROIDISM

Spontaneous myxedema is a chronic affection associated with gradual fibrosis and atrophy of the acini of the thyroid gland and characterized by impaired mentality, overgrowth of fat and connective tissue, and pronounced change in appearance. The disease occurs all over the world, but is most frequent in goitrous regions. It is usually seen in women at about the time of the menopause but approximately one eighth of the cases occur in men and a very small number in children. Of the cause of the thyroid shrinkage practically nothing is known; it is said that the disease has a familial tendency.

In the usual case of myxedema the first symptom is a gradually increasing mental sluggishness combined with a feeling of bodily weariness which is not appeased by any amount of resting. The face assumes a coarsened, masklike expression, with often a transverse furrow across the forehead and an area of brownish pigmentation over the cheeks. The skin is dry and scaly and the hair falls out. The false edematous deposits, which do not pit upon pressure, occur in all the subcutaneous tissues, making it appear as though the patient has stored up much fat; the extremities are chiefly affected, however. Lange (1944) ascribed this edema to a marked increase in capillary permeability which rapidly regressed under thyroid therapy; it will be interesting to see whether his findings are confirmed. The temperature is below normal, there is a secondary anemia and a reduction in pulse and basal metabolic rates, and

the patient complains of constipation, unusual sensitiveness to cold and pains in the muscles and joints. The cholesterol level in the blood is elevated in practically all cases. The occurrence of "myxedema heart" as a typical entity is now acknowledged by most observers: marked enlargement, slow feeble beat, increased circulation time, occasionally pericardial or pleural effusion, usually no gross evidences of failure—all resisting digitalis but clearing up promptly under thyroid therapy. Latterly, evidence has been accumulating to show that myxedematous individuals are unusually prone to develop arteriosclerosis, chronic nephritis, arthritis, fibrous myocarditis and coronary sclerosis, but since the age of onset of many of these conditions coincides closely with that of myxedema, it is going to require very careful work to establish the inter-relationship.

In recent years a number of observers have been calling attention to the probable frequency with which individuals are relegated to the scrap heap of "neurasthenia" when they are suffering from a mild hypothyroidism in which the full myxedematous picture never develops. Such patients may show one or more or none of the classical symptoms of real myxedema, but it is astonishing how many other symptoms that are not usually associated in a diagnostic connection with thyroid dysfunction will clear up on specific treatment. For instance they may be underweight and not sensitive to cold or suffering from a marked dryness of skin; indeed they may not even feel mentally sluggish, though they nearly always grow inordinately tired by the end of the day. Menstrual or abdominal disturbances of many types, habitual abortion or sterility, or rheumatic pains may bring them under observation. The diagnosis is more often made in women than in men, but Schwittay (1941) pointed out that this may be partially due to the fact that menstrual disturbances are objective signs which ultimately cause women to seek medical help. Thurman and Thompson concluded a number of years ago that if in suspected cases of hypothyroidism without frank myxedema the depression in basal metabolic rate is less than 21 per cent below the average normal, underfunction of the thyroid is usually not present. But that has not been the subsequent experience, at least here in the Great Lakes region; for example, Schwittay, describing his experience in Wisconsin, says the results of the therapeutic test are often as dramatic when the basal rate is −8 or −10 as when it is −25 or −30, and indeed this accords with the experience of Davis (1943), in Delaware, where he is finding much more hypothyroidism than had been suspected to be present.

THERAPY

In the summer of 1891, Murray described before the British Medical Association the first case of myxedema ever treated by the administration of the thyroid gland of the sheep. His patient, a woman of forty-six, regained good health and lived to be seventy-four, dying in 1919 of heart disease. Since the reporting of this classic case, many thousands of patients have been thus treated and cured, and it has now become apparent that such failures to restore the patient to complete health as do occur are due to one or more of the following factors:

(*a*) *The use of a nonpotent specimen of the drug.* Hunt, corroborated by Means (1933) and Lerman and Salter (1934), has shown that there may be a great variation in the strength of the drug as prepared by different manufacturers, a fact which certainly places the practitioner with his occasional case of this disease in a quandary. The only practicable solution of this difficulty

is to determine the dosage with a particular preparation solely upon the basis of therapeutic results. Thyroxin is more expensive than the desiccated gland substance and not as reliably effective; it may be given by mouth or parenterally.

(*b*) *The beginning of treatment too late in the disease.* It is the exceptional individual with far advanced myxedema who completely recovers under even the most careful treatment.

(*c*) *Lack of cooperation upon the part of the patient.* After a considerable degree of recovery has taken place very many individuals refuse to continue with the proper thyroid dosage required to complete and maintain their cure.

(*d*) *The careless taking of overdoses by patients,* who, having once experienced the resultant thyrotoxic symptoms, are evermore reluctant to take sufficient doses to maintain them in a normal condition.

It is the universal practice to administer thyroid substance in two stages: (1) initial dosage designed to restore the patient to a normal level of metabolism, and (2) maintenance dosage, which is the smallest amount necessary to keep the metabolism within normal limits.

Thyroid Dosage in Myxedema.—The patient is weighed and put to bed, or at least required to spend much of the time in bed during the initial stage of treatment, and the pulse is counted each morning by the patient or some member of the family at rising time; in this way a check on the basal pulse rate is obtained with the elimination of such factors as the influence of food and muscular activity. In the practice of some men dosage begins with 2 grains (0.12 Gm.) of thyroid substance three times daily for five days. Then the patient is weighed again and if only 2 or 3 pounds (0.9 or 1.4 Kg.) have been lost, and the pulse rate is not above 80 and there are no signs of overaction, such as palpitation, dyspnea, excessive warmth, dizziness or nausea, administration may continue until a normal pulse rate is obtained or such toxic symptoms appear. But this is drastic therapy and in the opinion of many men not wise. Thompson (1939) usually begins with a dose of only 1 grain (0.06 Gm.) daily and in individuals with arteriosclerosis or coronary disease he starts with only ½ grain (0.03 Gm.). Thereafter changes in dosage are made very gradually; in average cases in Thompson's experience 1½ to 2 grains (0.1 to 0.12 Gm.) have sufficed for maintenance; Shorr (1944) said that in no case of complete myxedema at the New York Hospital has more than 3 grains (0.2 Gm.) been required. Since thyroid substance acts very slowly there seems no point in giving divided dosage throughout the day, nor has any relationship been established between exercise and the replacement therapy required. Shorr has pointed out that since most cases of myxedema fall into the postmenopausal age group in which degenerative vascular changes may be expected, it is wise to bring the metabolic rate slowly up to normal in order very gradually to increase the amount of work required of the heart and the load upon the vessels.

Winkler *et al.* (1943), attempting to define as exactly as possible the relationship between thyroid dosage and metabolic response, found: (*a*) the myxedematous subject certainly does not react to thyroid medication with the mathematical predictability of a machine, factors other than thyroid medication obviously affecting the basal metabolic rate since it varies from time to time without change in the dose of thyroid; (*b*) dosage regularly lies between 1 and 3 grains (0.06–0.2 Gm.) daily with a leeway that is not more than a grain (0.06 Gm.) or so daily; (*c*) tolerance to dried thyroid substance apparently

never develops even after years of medication. Barnes (1942) has begun a very interesting study of the use of body temperature rather than the basal metabolic rate as a gauge for thyroid dosage.

Thyroid Dosage in Hypothyroidism without Myxedema.—The dosage here is about the same as in true myxedema. Seward (1935) reports that about half of his patients have been able to omit the drug for a few weeks now and then without myxedematous symptoms immediately returning. Hartsock (1936) makes the practical point that thyroid substance taken not later than mid-afternoon is not likely to induce difficulty in getting to sleep and palpitation as the patient lies down.

Auxiliary Therapy.—The eruptions or other reactions which sometimes accompany thyroid therapy in the beginning can at times be avoided by the simultaneous administration of small doses of the solution of potassium arsenite (Fowler's solution). Where there is an extreme degree of idiosyncrasy, desensitization must be attempted with minute doses—1/1000 grain daily to begin with and gradually increasing after a few days. Where this is not practicable the thyroid substance will have to be given intermittently in as large doses as can be tolerated. Paradoxically, it is sometimes necessary to use sedatives in the initial stage, particularly in the nervously unstable type of individual; barbiturates serve well here. A number of years ago Christian warned of the special need of digitalis in cases complicated by cardiac insufficiency, for as the myxedematous condition improves more work is demanded of the heart; anemia too should be corrected. In view of the great advances made in the field of the vitamin deficiencies in recent times, it seems to me that the diet of all these people should be thoroughly investigated.

SIMPLE GOITER

Simple goiter is a diffuse, symmetrical, noninflammatory enlargement of the thyroid gland which is caused by the distention of its alveoli by an excessive deposit of colloid. Since the earliest times the view has probably been held that the incidence of this affection is in some way associated with the water supply. The Chinese of fifteen centuries B.C., as well as the Greeks and Romans of the western Classical Age, have left attestations of this belief, and relatively recently "discovered" races, such as the natives of interior Africa and the American Indians, were also convinced of the relationship. However, it remained for the French chemist, Boussingault, to propose, in 1833, the hypothesis that it is an insufficiency of iodine in food and water that is the causative factor. Boussingault actually suggested the use of iodized salt in prevention, but his observations were apparently lost sight of, for when, in 1840, iodine prophylaxis was attempted in Switzerland, France and Italy, it seems to have been initiated by Chatin under the inspiration of Grange's "new" discovery of the iodine-goiter relationship. The present theory of the association of iodine starvation and colloid goiter is due to the painstaking researches of Marine and his associates and really constitutes a "new" discovery, for the work done during the middle of the last century had long since been forgotten. That goiter is most prevalent in regions where the water, soil or indigenous vegetables, cereals, fruits and milk are poorest in iodine, is now gener-

ally recognized. In Europe these regions correspond to the Carpathian, Alpine and Pyrenees mountain ranges; in England to a belt extending from Cornwall north-eastwards through Somerset and between the Cotswold and Chiltern Hills into Northamptonshire, whence it extends northwards into Derbyshire, Cumberland, West Durham and Northumberland, with offshoots extending from Wiltshire to the Isle of Wight, across Hereford into South Wales and across Cheshire into North Wales, and with a small area being found also where Sussex joins southwest Kent; in South America to the Andes plateau and an area in southeastern Brazil; and in North America to the region about the Great Lakes and the St. Lawrence River and the Cascade mountain region of Oregon, Washington and British Columbia, with less important foci in the Rocky Mountain states and those of the Upper Mississippi Valley. In Asia the principal endemic areas seem to be in the vast Himalayan mountain ranges, the province of Yunnan in China and the island of Formosa, though there are recent reports (Robertson, 1940) that Japanese occupation of parts of coastal China is robbing the hinterland of its coastal supply of iodine with the result that goiter is greatly increasing in the interior, which has now become dependent upon Yunnan for its salt supply. That residence near the sea is in itself a safeguard against the development of the disease, as would seem to be indicated by the relative infrequency of its occurrence along the Atlantic seaboard of the United States, is disproved by the fact of its great prevalence on the northern Pacific coast, in England, and also in New Zealand, in which latter country most of the habitations are coastal and none more than 100 miles inland. In accepting this relationship of iodine starvation to goiter it is necessary, however, to go a step further and postulate that the disease develops only in those in whom some other as yet unknown factor or factors are operating, for it would otherwise be impossible to account for the escape of many individuals in goitrous regions and the appearance of sporadic cases in non-goitrous regions. Present animal experimentation with goitrogenic diets will probably throw further light upon the subject.

Simple goiter develops most frequently at the age of puberty and more often in girls than boys; it also not uncommonly appears in women during pregnancy and lactation. The symptoms it causes are usually few or none, save the psychic disturbances consequent upon the disfigurement. A small proportion of goiters disappear spontaneously but most of them persist to some extent throughout life. When serious symptoms arise they are usually due to the displacement of the larynx and trachea, with disturbance of respiration, or to circulatory disturbances due to pressure upon contiguous nerves.

PROPHYLAXIS

Methods.—At the present time the prophylactic measures employed are the following:

(1) The administration of a tablet containing $\frac{1}{6}$ grain (0.01 Gm) of an organic iodine compound once a week throughout the school year (or throughout the duration of pregnancy). Such preparations contained in the 1944 N.N.R. are: iodocasein with chocolate, chocolate tablets iodostarine, oridine tablets, stearodine tablets.

(2) The addition during a period of two or three weeks twice a year of sufficient sodium iodide to the municipal water supply to bring the iodine content up to fifty parts per billion during that time.

(3) The use of iodized table salt. An advisory committee of the American

Medical Association has recommended that in all endemic regions a salt containing 0.01 per cent of iodine be employed (a recent analysis of 13 brands by the Wisconsin State Board of Health showed an average content of 0.014 per cent; of the 63 samples examined in Michigan, in 1939, none was found to contain less than 0.01 per cent—most manufacturers, however, advertise the content to be higher than this). It is recommended that this salt be used in cooking and at table by all persons throughout the year.

Efficacy of the Methods.—Iodine was first used on a large scale in the prevention of human goiter by Marine and Kimball in the school population of Akron, Ohio, in 1917. Of 2190 school girls who took iodine for three years, only 5 developed goiter, while of 2305 also observed for three years but who did not take iodine, 495 developed goiter. Since the publication of these studies numerous communities throughout the world have employed the prophylactic use of the element with a very high degree of success. It is the belief of those who have watched these studies most closely that under ideal conditions of cooperation the incidence of goiter in childhood and pregnancy could be reduced to practically nothing. Goiters developing *in utero* are also prevented. The studies of Hudson (1931) have shown that iodides given to the mother pass through the placenta and are absorbed by the thyroid of the fetus so that if a goitrous child is born of a mother who has received iodides throughout her pregnancy it is not because of a deficiency of iodine in the fetal thyroid.

Comparison of the Methods.—All three of the methods are effective but Kimball (1939) says that experience has shown the use of iodized table salt to be the most satisfactory and least expensive.

Danger.—The danger of inducing iodine thyrotoxicosis in adults who participate in any of the prophylactic measures is now conceded by practically all observers to be so small that it cannot be taken into practical account.

THERAPY

The treatment of simple goiter by the same methods as are employed in prophylaxis sometimes accomplishes an astonishing diminution or even total disappearance of the enlargement. However, the cases of long-standing goiter that are favorably affected are very few. Up to sixteen or seventeen years of age the response is better; in Marine and Kimball's studies in Akron, Ohio, of 1182 children with goiter at the first examination who took iodine, 773 thyroids decreased in size, while of the 1048 children with goiter at the first examination who did not take iodine, only 145 decreased in size.

ADENOMA

A certain number of goiters are nodular and are therefore, but perhaps erroneously, considered adenomatous. A few of these nodules have the structure of fetal thyroid and are assumed to arise from embryonal cell nests, but the great majority of them seem to be encapsulated masses of adult thyroid tissue. Many observers believe these nodules to represent areas of disorderly growth in response to some unknown stimulus, and that a state of hyperthyroidism can be initiated from such a nodule without diffuse involvement of the gland. However, the studies of Rienhoff, confirmed by both Dunhill

and Hertzler, have considerably influenced opinion—studies in which it was shown that the involutional changes occurring in the thyroid glands of patients with exophthalmic goiter who were undergoing remission revealed striking similarities to the histologic picture seen in nodular goiter; Cole and Womack have made the same observation in their experimental production of nodular goiter in dogs. This would make of these nodules neoplasms in no sense of the word but involutional bodies whose number and size depend upon the number of remissions and exacerbations in the gland. The fact that cases of so-called "toxic adenoma" sometimes develop may simply mean that the diagnosis of toxic adenoma is made during a particularly fulminating exacerbation in a gland that has undergone many milder exacerbations and remissions. The fact that exophthalmos is unusual in these cases need not set them apart as a separate type of thyrotoxicosis for most of the cases develop after the middle thirties, at which time this symptom is also unusual in the nonnodular cases.

THERAPY

Most surgeons believe that all nodular goiters should be removed because of the occasional development of malignancy on a nodular base, or because of the fact that thyrotoxicosis may appear later in life. Foster comments on this attitude as follows: "This appears a radical view in the face of the fact that discrete adenomata are not rarely palpable in the thyroids of elderly persons who had recognized an abnormal 'gland' in their necks years before. Considering the adequate supply of hazards in modern life it seems both conservative and judicious for the family physician to make an occasional examination of a young person with an adenoma of the thyroid, and reserve decision on developments." Schlesinger *et al.* (1938) say that after the age of fifty years nodules in the goiter are so common, especially in women, "as to be almost physiologic." Still, malignancy is malignancy, and since, as Clute and Albright (1936) reiterate, good scars and no mortality are to be expected after removal of a simple adenoma, the responsibility of advising against such removal is rather great. Lahey (1939) stresses the fact that the type of goiter most likely to become intrathoracic is the discrete adenoma of the lower pole of the thyroid.

Jackson and Freeman (1936) warn against giving iodine to patients with nontoxic adenomas, believing that "iodine hyperthyroidism" is sometimes induced; the subject is controversial, Means and Lerman (1935) notably being in disagreement with Jackson's viewpoint. In cases of established toxic adenoma not associated with the preceding use of iodine, Jackson advocates the use of the drug in preparation for and after operation, though he finds that only 62 per cent of the patients are benefited or not affected, while 38 per cent are made worse.

THYROTOXICOSIS

(*Exophthalmic Goiter, Graves' Disease, Basedow's Disease*)

Thyrotoxicosis is the name given to a peculiar complex of symptoms of which the chief are enlargement of the thyroid gland, an increase in the basal metabolic rate, a decrease in weight and strength, a characteristic nervous syndrome, exophthalmos usually, and a tendency to gastro-intestinal crises

of nausea and vomiting. Shirer (1933) has shown that there is a state of hypermotility of the gastro-intestinal tract, the degree of which, however, is no index of the severity of the disease. The classic description of the disease is that of Caleb Parry, in 1786, though the paper of Graves, in 1835, was the first to attract wide attention; Basedow described it again in 1840. Thyrotoxicosis occurs far more often in women than in men and principally between the ages of fifteen and thirty-five, no race being entirely exempt. The disease is believed to be of relatively infrequent occurrence throughout the world, but doubtless many mild cases are constantly being mistaken for neurasthenia, psychoneurosis and cardiac disorders unrelated to thyrotoxicosis. The belief that the disease is more frequent in large cities than in rural districts is not supported by authoritative statistical studies; likewise, the opinion that the incidence is highest in goitrous areas lacks substantiation.

The patients are usually restless—frequently making unnecessary purposeful movements—nervous and irritable long before any other disturbances are noted. The appetite often increases during this period and there is not infrequently a gain in weight. When the patient finally visits the physician, however, she usually presents the following signs and symptoms: loss of weight despite a normal or even increased appetite; rapid pulse rate, usually accompanied by palpitation and a low diastolic pressure or perhaps a slight systolic rise; a great emotionalism either of the depressed or exhilarated type, perhaps even with the development of a pronounced psychosis; muscular tremor, especially noticeable in the extended fingers, combined with easy muscular fatigue (a few cases of generalized myopathies directly associated with the disease have been reported); complaint of insomnia; excessive sweating and discomfort in warm weather; a basal metabolic rate much above the normal, and not uncommonly glycosuria and hyperglycemia and impaired dextrose tolerance; usually some degree of exophthalmos (in some cases the protrusion is illusory, being caused only by retraction of the upper lids); and the history of a number of attacks of nausea, vomiting and diarrhea, during which all the symptoms are much aggravated. Considerable thyroid enlargement is usual and some enlargement is detectable in practically all cases. Liver function is now known to be disturbed more often than was formerly believed, but Bartel's (1939) studies indicated that hyperthyroidism *per se* does not disturb kidney function. Blood iodine is elevated in some instances and there is a tendency toward low cholesterol and serum-protein levels; disturbances in creatine and calcium metabolism frequently occur. Hyperplasia of the thyroid tissue is the most frequent finding at autopsy, but it does not seem that this bears a constant relationship to the clinical symptomatology, for this hyperplastic state is compatible with a normal or even myxedematous condition. An increase in lymphoid tissues all over the body and hyperplasia of the thymus gland is found in most thyrotoxicosis autopsies. There are surprisingly many variations from the typical in this disease; Wohl, Lahey and others have many times directed attention toward cases that successfully masquerade as other entities with little to call attention to the underlying thyrotoxic disturbance, even an "apathetic" type being occasionally seen.

The etiology of this disease is still unknown, one school of observers holding that the occurrences in the thyroid gland are the primary cause of the abnormal state, the other that thyrotoxicosis is a general constitutional disease, perhaps originating in a disturbance of the autonomic nervous system or an imbalance in the endocrine system (particularly an excessive secretion of the thyrotropic

hormone of the anterior pituitary body), of which the thyroid symptoms are only a manifestation. The secondary etiologic role of acute or chronic infectious processes, fear, trauma, operative procedures, nervous strain, or acute nervous shock is affirmed and denied with equal fervor and authority. Occasionally a case, apparently precipitated by such a factor, will rather promptly subside upon removal of the thyroid, but in the vast majority of instances the course is a long one with remissions and relapses over many years; prediction of the duration of a remission, or the severity of a relapse, can never be made. A type of autonomic imbalance, differing from thyrotoxicosis by absence of asthenia, heightened metabolic rate and loss of weight, is usually looked upon as a separate entity. Moschcowitz and Bernstein (1944) are the latest of several observers to look upon the initial stage of Graves' disease and neurocirculatory asthenia as identical. A few men feel that thyrotoxicosis develops preponderantly in patients of the sensitive emotional type and they refer to a special hereditary predisposition as a "Graves' constitution," but I think that Fitz (1944) expressed the consensus in stating that this position is not justified.

THERAPY

There is a new drug, thiouracil, available nowadays for the treatment of thyrotoxicosis and it will be duly described below, but the experience with it to date is still so relatively slight that I certainly do not feel warranted in curtailing my description of the older classical types of treatment, namely, the surgical, the medical and the roentgenologic. Parenthetically I may add that investigations with the radioactive isotopes of iodine have given great promise, but War II interrupted these studies. In the surgical, the medical and the roentgenologic types of treatment the employment of rest and a full diet are essential to success. Surgeons do not like to operate unless the patient has gone through a preparatory period of rest and full diet; roentgenologists do undertake the handling of cases without such a preliminary period but only because their results are slowly obtained, and they insist upon the institution of a regimen of rest and full diet concomitantly with their course of treatments; and, as regards the medical type of treatment, rest and full diet are practically the whole of the therapy.

"Medical" Treatment with Rest and Full Feeding.—This is the type of treatment most frequently employed, yet it is the one about whose results we know least. It consists in instituting primarily a period of complete rest and full feeding, to be followed by a gradual return to as near full activities as can be accomplished, the sole object and aim of the method being to promote an earlier economic and social rehabilitation than occurs in the entirely untreated case. It is of course based upon the assumption that thyrotoxicosis is a constitutional disease with a marked tendency to be self-limited. The patient is put at complete rest in bed and the attempt is made to accomplish complete mental rest as well. Both these objectives are often best attained in a hospital but as a matter of fact most patients are treated in the home. Success will hardly crown the attempt unless the economic and other stresses under which the patient is laboring are materially reduced. Often such a reduction can be accomplished by merely denying the access of certain persons to the patient, but usually the difficulty is not so easily overcome. The employment of sedatives is nearly always necessary at least in the beginning; these drugs are discussed in Insomnia. Of course the use of such stimulants as coffee and other caffeine-containing beverages should be strictly forbidden.

Full feeding in these cases means simply giving the patient all she will eat. Usually the appetite is quite ravenous in the beginning and is best satisfied by numerous small feedings between the three full meals. The theoretical value of holding down the protein content of the diet because of its specific dynamic effect was possibly to some extent supported by Jones' (1940) observation that thyrotoxic individuals tend constantly to prefer a diet low in protein. The advisability of a high carbohydrate diet is obvious since fuel is being so rapidly consumed in the body.

In fortunate instances, the basal metabolic rate and the pulse rate gradually fall and the patient's subjective symptoms markedly recede. Under the circumstances in which this type of treatment is employed, accurate and reliable basal metabolic studies with a "machine" cannot usually be made, but many men find that the employment of one or other of the formulae utilizing pulse rate and pulse pressure serves them as a crude, second-best substitute. The simplest of the lot, that of Gale and Gale (1931), can be conveniently memorized and used; it was found by Comroe (1935) to give results not significantly less accurate than those obtained with the more elaborate calculations of Read and Barnett. The Gale formula, to be applied under basal conditions, is: P.R. + P.P. −111 = B.M.R., where P.R. is the pulse rate, P.P. is the pulse pressure (difference between systolic and diastolic pressures), and B.M.R. is the basal metabolic rate which is being sought.

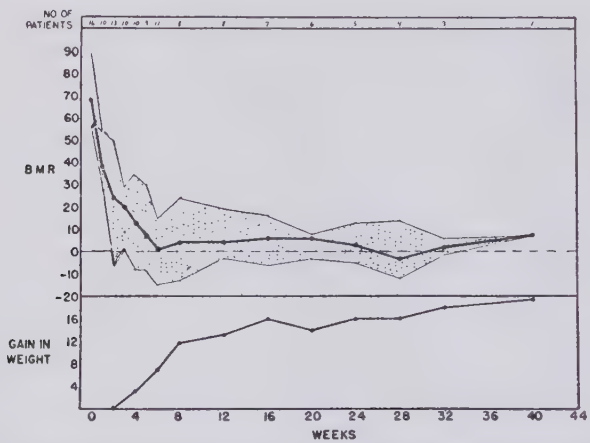
After a variable number of weeks, *i.e.*, when it is no longer felt that anything is being accomplished by further insistence upon absolute rest, the attempt is made to return the individual slowly to her former economic status. It is freely admitted by those who champion this type of treatment that a full rehabilitation is not always accomplished, perhaps is not accomplished even in the majority of cases. I can only repeat that we have little statistical evidence of the value of this "medical" treatment. The reasons for this are obvious: it is principally employed by general practitioners who have not the follow-up facilities of the large clinics; it is not often persisted in until the program is fully executed for the reason that many individuals feel forced to resume their full activities as soon as moderate subsidence of symptoms makes this possible; and, finally, many patients who begin such a course of treatment weary of the time consumed and yield to the promise of quicker relief held out by the surgeon.

Vitamins.—Studies in recent years are pointing to the advisability of using supplementary vitamins in these patients. Womack, reviewing the matter in 1940, felt the chief indications to be for vitamins A and B. That would mean a fish liver oil or carotene to provide vitamin A, thiamine for B_1, and dried brewers' yeast or at least nicotinic acid (niacin) and riboflavin for the B_2 complex. Williams *et al.* (1943) found that in a majority of forty unselected thyrotoxic subjects, the level of thiamine in the blood was below normal and the administration of thiamine was distinctly advantageous as adjunctive therapy. See index for methods of administering the vitamins.

Iodine.—Regarding the inclusion of iodine in this regimen, I can only say that as the years pass and convincing evidence of its safety fails to be produced, one cannot avoid becoming skeptical of the wisdom of its inclusion. I know a few men who claim that their results justify them in using the drug in "medically" treated cases—in small or large doses continuously or intermittently, but usually the latter, as judgment indicates. However, surgeons are increasingly complaining that many patients are made worse by this practice, and

that they are thus deprived of the opportunity to operate at the optimal time. Perhaps many men are not using the drug with intelligence but just administering it in a routine fashion and letting it go at that. I do not know. Certainly it seems that the surgeons can back their warnings with strongly presumptive evidence; still, I feel that the whole truth is not yet known here, but am nowadays far from certain, since thyroid surgery has attained its fine peak of perfection, that it is worth trying to ferret out. In short, it would seem well in the present state of our knowledge to leave iodine for pre- and postoperative use in surgically treated cases.

Thiouracil.—This new agent was introduced by Astwood, of the Peter Bent Brigham Hospital in Boston, in early 1943. Its ability to effect a reduction in the basal metabolic rate and an increase in weight, both of which are well sustained, is sharply presented in the accompanying figure. The current hypothesis in explanation of the action of the drug is that it prevents the utilization of iodine in the synthesis of thyroid hormone within the thyroid gland, which cessation of thyroid hormone production in turn stimulates the thyro-



The changes in metabolic rate and weight in association with the thiouracil treatment of 16 patients with marked thyrotoxicosis. (Williams and Clute, 1944.)

tropic activity of the pituitary, causing further hyperplasia of the thyroid, the latter however not being able to overcome the thiouracil block of the active thyroid hormone production. In addition to its salutary effects upon the symptomatic evidences of thyrotoxicosis, it has been shown by Sloan and Shorr (1944) to have effects upon the disturbances of calcium, phosphorus, nitrogen and creatine metabolism occurring in the disease, comparable in degree to the beneficial results following successful subtotal thyroidectomy or iodine remission.

The findings of Williams and Clute (1944) of the Boston City Hospital, based upon the employment of the drug in 72 cases, will be analyzed in what follows:

Advantages.—The authors' experience with the drug indicated that it can be depended upon in essentially all cases to lower the basal metabolic rate to a normal range and to maintain it at that level so long as treatment is continued. Associated with this effect upon the basal metabolic rate is a clinical remission of the disease, with disappearance of tachycardia, hyperidrosis,

nervousness, diarrhea, weight loss and other toxic manifestations. In 4 patients who discontinued therapy after a few months, a relapse occurred in about three weeks, but remission followed the return to thiouracil. In the chart published with the kind permission of Drs. Williams and Clute, it is seen how rapidly improvement begins and how progressive it is; indeed many patients in this series maintained that marked improvement had occurred within twenty-four to forty-eight hours after first taking thiouracil, but the authors felt this rapid change may have been due at least in part to the mild sedative effects of the drug as well as to its psychologic effect. In most cases it was found that the great dependability of the agent in controlling toxicity in the patient not only made hospitalization unnecessary but actually permitted most of the individuals to continue regularly with their work. It was felt of course that patients undergoing this treatment must maintain close contact with the physician nevertheless. The matters of chronic complications and the development of therapeutic unresponsiveness to the drug must be borne in mind since these are possibilities that have not as yet been explored.

Dosage.—The dosage plan followed in this series was the following: 3 grains (0.2 Gm.) by mouth three times daily for the first two weeks, followed by 3 grains (0.2 Gm.) twice daily until the metabolism is normal, and then 1½ grains (0.1 Gm.) twice daily until the basal rate has been maintained well within normal limits for several weeks, when the dosage was reduced to 1½ grains (0.1 Gm.) daily. Very few patients required larger doses than the above and a number of them obtained the effect with smaller ones. In any case, since thiouracil is rapidly absorbed and excreted, it was felt better to give two or three suitably reduced doses per day than only one. Indeed, in a later publication Williams (1944) said that he is now giving the drug five times daily during the first two weeks, 0.1 Gm. at 7 A.M., 11 A.M., 3 P.M., 7 P.M. and 0.2 Gm. at bedtime; at the end of two weeks the dosage is reduced to 0.4 Gm. daily given in doses of 0.1 Gm. at intervals of five hours; at the end of four weeks the daily dosage is reduced to 0.3 Gm., and after six weeks to 0.2 Gm.; after twelve weeks it is reduced to 0.1 Gm. provided the basal metabolic rate is approximately 0 or below and there are no clinical manifestations of thyrotoxicity. It was found that routine estimation of the thiouracil content of the blood and urine was of no definite aid in treatment, since most of the tissues can readily break down thiouracil and thus interfere with its accumulation in the body of normal subjects as well as of patients with severe disease of the heart, kidneys, or liver.

Thiouracil Plus Iodine.—Patients who had previously been taking iodides responded more slowly to thiouracil than did those who had not had any, and indeed in some cases there was actually an exacerbation of the symptoms if thiouracil was suddenly exchanged for iodide. The authors therefore formed the practice of overlapping the treatments for about two weeks when patients were changed from iodide to thiouracil therapy. The possibility that iodide given in conjunction with thiouracil might possibly enhance the effectiveness of the latter through increasing the storage of thiouracil in the thyroid is now being investigated by Williams and his associates.

Effect upon Subsequent Thyroidectomy.—In none of the patients in this series was a thyroidectomy performed because of any evidence that the metabolic rate would not return to normal with the use of thiouracil alone. Nevertheless, for various other reasons, 22 of the patients did come to operation. There were no greater technical difficulties in the removal of the gland after thiouracil

therapy than exist after iodide therapy except for slightly more vascularity and friability of the tissues; Rienhoff (1944) has also commented upon the fact that the thiouracil gland is a more difficult one to operate on from the standpoint of hemostasis.

Effect on Goiter and Exophthalmos.—In most of the patients a distinct decrease in the size of the thyroid gland was observed after more than six weeks of treatment; in twenty-one cases this decrease was from 33 to 66 per cent in extent and in a few cases there was a return to an essentially normal size. However, in 11 of the patients there occurred an increase of the size of the gland during the first few weeks of treatment, and the consistence of these glands as well as those of some other patients became firmer soon after thiouracil was started; in 2 cases the gland was distinctly larger after several months of treatment than it was at the beginning of the therapy. Since desiccated thyroid not only inhibits the production of thyrotropic hormone but also exerts a diuretic effect, it was considered that the administration of the dried gland might be effective in these cases—continuing the thiouracil dosage at a sufficient level to maintain a normal metabolic rate, desiccated thyroid was given in doses of 8 to 24 grains (0.5 to 1.5 Gm.) daily; in most of the 9 cases in which this combined treatment was tried it proved to be of advantage.

All the patients who exhibited a stare and widened palpebral fissures experienced distinct improvement in these disturbances under the drug and many stated that their eyes were "looking normal again." However, in 5 patients who initially exhibited changes in the orbits characteristic of those found with malignant exophthalmos, the manifestations became worse during the first few weeks of treatment with thiouracil and in one case they became severe, the patient developing marked palpebral edema, conjunctival injection and chemosis, marked lacrimation and severe corneal ulcers. Thiouracil dosage was reduced in these cases and thyroid substance was administered, but it is not stated how effective this alteration in the therapy was.

Toxic Reactions.—Untoward reactions of some sort occurred in 13 of the 72 patients. There were a number of instances of leukopenia and granulocytopenia, but in only 2 patients did a severe agranulocytosis develop. The condition was discovered at the end of six weeks in one patient, who recovered despite the fact that only a few granulocytes were present for a period of a week; in the other patient the white cell count dropped to 3200, with 20 per cent granulocytes, only a few days after beginning thiouracil treatment, but in this patient in spite of continued therapy the white cell count returned to normal and the granulocytes increased to 50 per cent, the patient subsequently taking thiouracil for six months and remaining in good health. Welshman (1944), Newcomb and Deane (1944), and several other observers have reported cases of agranulocytosis, Newcomb and Deane's patient developing thrombopenia also. The only report of a fatal agranulocytosis that has come to my attention is that of Kahn and Stock (1944), whose patient developed the reaction on the forty-fourth day of medication with thiouracil and died five days later despite the fact that administration of the drug was immediately stopped upon the first appearance of symptoms. Upon the basis of animal experimentation, Goldsmith *et al.* (1944) suggested the trial of solubilized liver (fraction L) in the prevention and treatment of the granulocytopenia. Four of the patients in Williams and Clute's series developed a morbilliform rash, associated with itching, but this disappeared in spite of continued treatment. Three others developed moderately severe urticaria. One of these patients

discontinued the drug for three days and then resumed it without recurrence. Another with urticaria developed painful, swollen and stiff joints lasting one week, and following this episode iodide therapy was substituted. The third patient developed urticaria and fever after eight months of thiouracil therapy, and a thyroidectomy was then performed. Six of the patients developed swelling of the legs that was not associated with hypoproteinemia, cardiac failure, or evidence of renal damage, and the data obtained in these and some other patients indicated to the authors that thiouracil in certain dosages may cause a retention of sodium chloride and water. A decrease in the carbon dioxide-combining power of the blood was also found in a few of these patients, but these changes disappeared in spite of continued therapy. Two patients experienced nausea and vomiting during the first week of treatment, but these symptoms disappeared without stopping the medication. Another patient had swelling and soreness of the submaxillary salivary glands which subsided without alteration of the treatment. Serious toxic manifestations, consisting of one or more of the following, occurred in 3 of the 21 cases of Paschkis *et al.* (1944) and in about 10 per cent of the 61 cases of Astwood (1944): cutaneous eruptions, fever, arthralgia, granulocytopenia and jaundice.

Thiouracil in Preparation for Operation.—Williams and Clute feel that thiouracil in preoperative preparation has the advantage over iodine of dependability in causing a disappearance of the toxic manifestations of this disease in essentially every case, provided that treatment is continued for several weeks, and that because of this dependability the patient may be permitted in most cases to perform a part or all of his usual activities during the period of preparation for the operation. They stressed, however, the necessity for adequate rest and full feeding during this interval. Further, since thiouracil decreases the quantity of thyroxin in the gland they feel that in cases treated with this drug there is potentially less thyroxin to get into the blood stream at the time of operation than in cases treated with potassium iodide. It is my own opinion, however, that much water must flow over the dam before this question may be considered settled.

Indications for Operative Treatment.—Since it is still far too early to know what effect thiouracil is going to have upon the picture of Graves' disease as a whole, I can only state here the viewpoint of careful observers prior to the advent of this new drug. Lahey, some years ago, stated that it was the definite conviction of himself and his associates at the Clinic that subtotal thyroidectomy is advisable in all patients who show no progressive and convincingly obvious improvement after three to four weeks of nonoperative treatment; he feels that if all observers will not go so far, at least few will reasonably disagree with the position that all patients in whom the disease is becoming intense should be immediately operated upon, such intensification being indicated by progressively rising pulse rate and progressive loss of weight in a patient at rest and on full feeding. Intercurrent infection increases the severity of symptoms, often with startling suddenness. Lahey also felt that any patient with cardiac damage, as indicated by mild failures or arrhythmia, should be immediately prepared for surgery and operated upon without preliminary trial of nonoperative measures; the complications of diabetes or pregnancy, either of which seriously adds to the risk of acute crisis, call for the same treatment. Lastly, any change in a patient's psychic state should be accepted as an indication of the onset of a possibly serious thyroid state, which nothing so certainly foretells as the appearance of diarrhea and vomiting. With regard

to so-called "iodine-fast" patients, *i.e.*, patients still quite toxic after several weeks of iodine therapy, Lahey (1939) was of the opinion that it is usually advisable to perform a reasonably immediate, graded, partial thyroidectomy, the two-stage operation being less dangerous than taking such patients off iodine and waiting. On this latter point, however, Kearns and Starr (1942) took a quite opposite stand, saying that the best thing to do with iodine-fast patients is gradually to get them off iodine through a period of some days or weeks and then to maintain them iodine-free, attempting to control the exaggerated symptoms with bed rest and sedation and possibly x-ray, and then trying iodinization again.

In preparing patients for operation it is probably the usual custom to give 10 minims (0.6 cc.) of compound solution of iodine (Lugol's solution) three times daily, but this treatment must be highly individualized.

Treatment of Thyroid Crises.—By the term "crisis" is meant severe exacerbation of all the symptoms of thyrotoxicosis. The metabolism, fever and pulse rate rise very high, nausea, vomiting, and often diarrhea are present, and excitement and restlessness not infrequently reach maniacal proportions. The administration of large amounts of fluid, dextrose and iodine is indicated here. Lahey writes as follows regarding the treatment during crisis:

"The best management of this state of severe hyperthyroidism is preventative; that is, to submit patients with hyperthyroidism to surgery early, before such a severe state can occur. The next best treatment of this condition is to recognize the earliest signs of its possible appearance and to introduce intravenously 40 to 60 drops of 5 per cent glucose and fluids per minute constantly day and night, together with the frequent intravenous administration of 50 per cent glucose, the patient having from 500 to 800 grams of glucose in the twenty-four hours. This is best introduced into the saphenous vein just above the ankle, as delirious patients are less annoyed by this and make fewer movements with their legs than with their arms. No attempt should be made to warm the solution. We have for a number of years put 50 drops of Lugol's solution in the 1000 cubic centimeters of fluid to be introduced intravenously, and have found it a positive, satisfactory, and safe way to get iodine into these vomiting and delirious patients."

Of course in many instances the patient is able to cooperate to some extent and even to retain some fluid swallowed; in such cases it may suffice to give the iodine by mouth, giving as much as 100 to 200 cc. of Lugol's solution in the first twenty-four hours. But in any case get large amounts of readily assimilable carbohydrate into these patients, and don't forget the vitamins!

Hyperthermia must often be combated also. Means (1939) says that usually cold packs or sponging do not suffice; the ice pack or ice bath has to be used.

Lahey does not subscribe to the opinion that to operate upon the patient who has recently recovered from a crisis is to court disaster. He believes that these patients having been relieved of their immediate danger by the checking of diarrhea and vomiting should be placed on a high carbohydrate diet for two or three weeks and operated upon, usually by the 2-stage method: right subtotal hemithyroidectomy, and at the end of six weeks, left subtotal thyroidectomy.

Treatment of Cardiac Complications.—In some instances of congestive failure and auricular fibrillation in thyrotoxicosis only operation will restore compensation, but in other cases digitalis will be slowly helpful, particularly if it is used in conjunction with iodine. In the treatment of the tachycardia

that is a distinguishing feature of the disease, and for the relief of palpitation that so often distresses the patient, digitalis is useless. Some men find quinidine, or one of the quinine salts, helpful in a dose of 2 grains (0.12 Gm.) several times daily, but Gold (1944) finds neither of these agents of value. For temporarily lowering the pulse rate for a few hours, Noble and Chen (1936) found thevetin useful, especially when given just prior to operation; the dosage in their small series of cases was 3 to 9 cat units, administered intravenously.

Treatment Following Operation.—Hyman (1940) probably expressed the consensus when he said that at once upon completion of the operation an intravenous drip of 5 per cent dextrose in saline (with distilled water substituted for saline after the first liter) should be instituted; certainly there can be no doubt of the protective action of this carbohydrate upon the liver. Schnedorf *et al.* (1941) found that oxygen therapy exerts a sedative effect upon the patient, facilitates aeration in the lungs, and slows the heart rate and reduces the temperature. Hyman said also that from 0.5 to 4 cc. daily of Lugol's solution should be got into the patient, either by mouth or through addition to the drip, for the first few postoperative days. Doubtless here too he expressed the consensus, but Davison and Aries (1939) latterly have been questioning the advisability of the routine use of iodine after subtotal thyroidectomy, pointing out that iodine acts only upon thyroxin in the gland and that with the gland gone it cannot be expected to combat thyroxin out in the blood stream and tissues; the patients treated postoperatively without iodine in their small series seemed to do as well as those given the drug. However, until the position of Davison and Aries is substantiated by further studies, iodine will probably continue to be used, especially in the effort to combat the mild symptoms of thyrotoxicosis which often persist for some months after discharge from the hospital. Cope and Welch (1942) said that iodine may be omitted if the metabolic rate is below normal within two weeks after operation; otherwise, it should be continued until it is certain that a normal or a subnormal metabolic rate has been established. Shorr (1944) said that it is the practice in his clinic at the New York Hospital to give iodine postoperatively for a year in every instance; his reasons for the continuance of iodine therapy were the following: (*a*) operation does not eliminate the basic cause of the disease; (*b*) involution of the residual hyperplastic thyroid tissue is promoted; (*c*) iodine promotes "stabilization" of the disease which may take as long as three or four years after operation. Small rations of iodine are usually given, such as 3 grains (0.2 Gm.) of potassium iodide or 15 minims (1 cc.) of Lugol, once daily or less; indeed, Shorr said that 1 cc. of the syrup of hydriodic acid or 1 minim of Lugol is quite sufficient. Lugol's may be acceptably given in cool water or milk, or in grape or orange juice, or dropped on a piece of bread. Potassium iodide is well prescribed in syrup of raspberry; the following contains 3 grains per teaspoonful:

℞	Potassium iodide	ʒiss	6.0
	Syrup of raspberry (N.F.) to make	℥iv	120.0
	Label: Teaspoonful in water as directed.		

Jackson is firmly convinced that coffee is definitely harmful to these patients, and doubtless many men agree with him. Wilson and Mayo (1940) reported the incidence of postoperative myxedema following 15,000 thyroidectomies at the Mayo Clinic to be 1.2 per cent. Postoperative tetany is very rare; see Tetany for treatment.

Serious persistence or recurrence of symptoms, or marked regrowth of goiter, requires a second or even a third operation, possibly preceded by a trial of roentgen therapy; in Berlin and Gargill's (1940) series of 235 cases, the incidence of persistent or recurrent thyrotoxicosis after operation was 5.1 per cent, about as low figures as one finds in the literature. Crile's advocacy of denervation of the adrenals found few supporters in conservative groups; Rogoff (1936) reported a case of Addison's disease following such surgical tinkering.

X-ray Treatment.—Irradiation of the thyroid by those skilled in the use of this weapon can claim the following advantages over surgery: (*a*) The procedure is simple and will usually be accepted by all classes of patients. (*b*) Mild reactions, characterized by nausea, vomiting and malaise, and lasting only twenty-four to forty-eight hours, are rare and the preliminary studies of Bean *et al.* (1944) indicate that these symptoms may be prevented or reduced in severity by giving supplements of nicotinic acid (niacin) or thiamine for a few days before irradiation. (Rose and Wolferth's, 1941, three cases of mediastinocardiac reaction are unique in the literature so far.) (*c*) Ambulatory patients, who cannot or will not give up their usual activities, can be treated just as well as the bedfast. (*d*) Patients are not subjected to the psychic trauma of the preparation for operation. (*e*) In the event of failure it may still be followed by surgery since the alleged production of dense adhesions apparently does not increase the operative difficulties to a degree that is of any moment at all. (*f*) There is no appreciable mortality chargeable against the method. Soley and Stone (1942) obtained marked improvement or complete relief in 33 of their 43 adult patients, which they feel to be as good results as a surgeon achieves. However, upon the whole, combined medical and surgical treatment is undoubtedly preferred by most men, some even agreeing with Hyman (1940) who said that whatever effect is produced by roentgen therapy is due to spontaneous remission or psychotherapy; but there is no blinking the fact that present enthusiasm for operative approach is based upon the results obtainable only in certain clinics where teamwork has been developed to the highest point. In the rare cases of toxic goiter in children under adolescence, the consensus is against early operation. Rose *et al.* (1935) felt that the record justified a careful trial of roentgen therapy in these cases; Poulton and Watt (1938), in England, also stressed its value in young patients.

Many roentgenologists believe that patients with hyperthyroidism who are to have radiation therapy should not previously receive iodine since it is a state of hyperactivity in the thyroid cells which makes them susceptible to the action of the roentgen ray. Pfahler (1942) expressed himself as firmly of this opinion, but Soley and Stone (1942) said that their experience permitted neither confirmation nor refutation of the idea.

ADDISON'S DISEASE

This disease, of which only about 300 to 400 cases are annually reported in the United States, is seen almost exclusively in adults in the middle period of life. It occurs in two distinct phases, the characteristics of which are the following: *Chronic phase:* the patient is asthenic, has lost weight, is hypo-

tensive, complains of vague digestive disturbances, and possibly manifests hypoglycemic reactions, while the heart is sometimes found to be reduced in size; but most importantly he exhibits dirty grayish-brown hyperpigmentation of the exposed surfaces and often, sometimes exclusively, of the genitalia, anus, axillae, nipples, lips, tongue and buccal mucosa. Pigmentation is greatest over bony prominences and scars and there is often black freckling of the shoulders and neck. *Critical phase:* the patient manifests, usually suddenly, the symptoms of suprarenal insufficiency; *i.e.*, anorexia, nausea, vomiting, diarrhea and circulatory collapse. Harrop, Loeb and their associates have shown that these crises are associated with the loss, chiefly in the urine, of large amounts of sodium chloride, the loss of sodium being greater than of chlorine. This sodium chloride loss is accompanied by blood concentration, high rise of serum potassium and of nitrogenous waste products, and reduction of the total base and carbon dioxide-combining power of the blood.

Harrop (1933) suggested sodium chloride restriction to precipitate crisis in order to facilitate diagnosis in the chronic phase; subsequent adoption of the suggestion of Wilder (1937) and his associates, namely, that potassium intake be kept high during the test, has added greatly to its usefulness, but there is now full recognition that the test is dangerous and should only be conducted in hospital where there is adequate provision for emergency therapy.

Addison's disease is due to depression or destruction of one or both of the suprarenal glands. According to Snell (1935), in 80 per cent of cases there is fibrocaseous tuberculosis of the glands (Sodeman, 1939, placed the proportion at 90 per cent, and Thorn, 1944, at only 50 per cent) and in the remaining 20 per cent of cases atrophy of the glands of unknown etiology; very rarely carcinoma, gumma, hemorrhage, infarction, mycosis fungoides, or chronic inflammatory changes with fibrosis of the glands have been associated with the disease in an apparent etiologic role. Snell says that in his experience at the Mayo Clinic about 1 patient in 3 has had demonstrable tuberculosis elsewhere in the body and 1 in 4 roentgenologically demonstrable suprarenal calcification. According to Kendall's (1935) showing, individuals with this disease die as the result of the development and extension of tuberculosis elsewhere in the body if they do not succumb early to the tuberculous suprarenal involvement.

THERAPY

Sodium Chloride and the Low Potassium Diet.—Of the value of a high sodium chloride intake there can be no doubt. The average daily salt intake, which in the United States is probably 6 Gm., is often augmented by an additional 6 to 20 Gm., taken in enteric-coated tablets. During crises of course large amounts of saline are administered intravenously. Wilder (1937) and his associates at the Mayo Clinic made a valuable contribution in showing that even with the administration of as much sodium as is contained in 18 Gm. of sodium chloride and 5 Gm. of sodium citrate, crisis may develop unless the potassium in the diet is kept considerably below the normal 4 Gm. intake. They proposed, and many others have subsequently used, the low potassium diet in Table 14. The following substances must be prescribed as supplements to this diet: calcium phosphate, an iron salt, thiamine (vitamin B_1), and the principal available ingredients of the vitamin B_2 complex, namely, nicotinic acid and riboflavin (see Index for methods of employing all these agents).

Foods to be absolutely avoided, according to Loeb (1941), are soups, broths, gravies, catsup, dried fruits and vegetables, bran and molasses. Meats and

vegetables should be cut into small pieces and cooked in 6 to 8 volumes of water.

Desoxycorticosterone.—Patients who cannot be reasonably well controlled by the use of sodium chloride and a low potassium diet must be treated with desoxycorticosterone acetate in addition, this agent being a natural steroid of the adrenal cortex which was synthesized by Steiger and Reichstein, in 1937.

Effect.—This agent affects almost exclusively electrolyte and water metabolism. The most noticeable and immediate effect is a gain in weight associated with the retention of sodium chloride and water; indeed, failure to gain weight within forty to seventy hours indicates insufficient dosage. There is a fall in serum potassium to a very low level, kidney function is improved, the

TABLE 14.—LOW POTASSIUM DIET (WILDER ET AL.)

Potassium, 1.6 Gm.; protein, 57 Gm.; calories, 2350

Food.	Gm.	Approximate measures.
Breakfast		
Orange juice	100	½ glass
Cornflakes	15	1 serving
Egg	50	1
Bread	50	2 slices
Butter	20	2 squares
Cream, 40 per cent fat	75	⅜ cup
Coffee if desired		
Dinner		
Beef tenderloin (weight uncooked)	70	1 average serving
Potato, thrice boiled	100	1 average serving
Carrots	25	1 small serving
Celery	25	2 celery hearts
Grapefruit	55	4 sections
Bread	50	2 slices
Butter	25	2½ squares
Cream, 40 per cent fat	20	1 tablespoonful
Tea or coffee if desired		
Supper		
Cheese	40	2 cubic inches
Rice (weight dry)	25	1 average serving
Tomato	50	½ average serving
French dressing	15	1 tablespoonful
Apple	80	¾ average size
Bread	50	2 slices
Butter	25	2½ squares
Cream, 40 per cent fat	20	1 tablespoonful
Tea or coffee if desired		

patient feels, looks and behaves much better. The blood pressure may rise very rapidly but it often requires weeks to attain a normal level. As the condition improves the size of the heart increases; indeed McGavack (1942) proposes the study of heart size as the most reliable guide to therapy. Complete disappearance of pigmentation has not been recorded. The action of the hormone is further incomplete in that it does not correct the disturbance in carbohydrate metabolism. Thorn (1944), and others, have found that the addition of compound E (Kendall) does correct this disturbance but this product is not commercially available.

Administration.—In 1941, Thorn advocated the maintenance of a daily sodium chloride supplement constant at 5 Gm., but by 1944 he had altered

his position in view of the fact that some clinicians prefer not to use sodium chloride in conjunction with desoxycorticosterone at all, the reason being the agent's potency in effecting the retention of sodium and chloride. Thorn says it is now his practice to begin therapy with 2.5 mg. of desoxycorticosterone acetate injected once daily and a 1 Gm. tablet of sodium chloride (enteric coated) three times daily with meals. After the patient has been maintained in good condition on these injections for two or three months, pellets of the crystalline hormone may be implanted subcutaneously, implanting 1 pellet of 125 mg. for each 0.5 mg. of hormone required by daily injection, the pellets usually providing effective therapy for approximately twelve months. Thorn describes the technic of implantation as follows: "The infrascapular region posteriorly is usually selected for pellet implantation. Strict asepsis is observed. The operative field is now prepared with iodine and alcohol and the site of the incision is infiltrated with procaine 1:200 solution. A transverse incision 2 to 4 cm. in length is made a few centimeters below the inferior spine of the scapula. With blunt dissection a number of small pockets, 2 to 3 cm. in depth, are prepared in the subcutaneous tissues. The opening of each pocket is held far enough apart by a nasal dilator to permit pellets to be dropped gently to the bottom of the pocket without the use of force. This is important, for if the opening into the pocket is too small a fragile pellet can easily be crushed by the force used to insert it; furthermore if the pocket is not deep enough the pellet may be extruded subsequently through the incision. The wound is closed with subcuticular sutures of fine black silk. It is possible to insert as many as 10 to 15 pellets through a single incision. Di Maio has recently described a modification of this technique which has the advantage of a smaller incision. A trocar is employed to implant the pellets in a row at some distance from the margin of the incision." Anderson *et al.* (1940), confirmed by Turnoff and Rowntree (1941), found sublingual therapy satisfactory; the latter's patients were given 1 mg. (6 drops) of the hormone in propylene glycol under the tongue six or seven times daily, expectorating the preparation after fifteen minutes. Dunlop (1943) also found this method effective but very cumbersome and wasteful; he also administered the agent effectively sublabially in tablets, but thought this also a wasteful though convenient method.

Overaction and Precautions.—Excessive edema may occur and may be counteracted by reduction in dosage of hormone or sodium chloride, not both simultaneously for fear of provoking crisis. Hypertension seems extremely likely to occur (Perera *et al.*, 1944, observed this development in 8 of their 24 patients) and to be accompanied by signs of serious cardiac overwork; dosage adjustment again is said to handle this situation; Currens and White's (1944) two patients responded well to digitalis. Hypoglycemic reactions are particularly likely to occur during acute infectious or gastro-intestinal disturbances; Shipley (1944) makes the point that fasting is dangerous for these patients. Hot weather, according to Ferrebee (1941), is likely to raise the requirement for hormone. Excessively low serum potassium levels so often occur in connection with this therapy that Tooke *et al.* (1940) were led to investigate their significance from the clinical standpoint and found that it became possible to administer the hormone practically without danger if the diet were *not* kept low in potassium; indeed, in some instances it even seemed advisable to supplement a normal diet with some additional potassium in the form of potassium citrate. Wilder (1940) carefully pointed out that this dietary reversal applies only to patients receiving desoxycorticosterone therapy and not to

those being treated with salt alone, which latter still require the low potassium diet.

Cortin.—The preparation of the adrenal cortical hormone dates from the work of Rogoff and Stewart, and Hartman independently, in 1927, with subsequent refinements in methods by Hartman, and Swingle and Pfiffner. "Cortin" preparations are commercially available, but the dosage is very high, the cost is absolutely prohibitive save for a very few individuals (Thorn, 1944, says that most patients will require 10 to 30 cc. intramuscularly per day at a cost of three dollars to ten dollars), and it has not been demonstrated to the satisfaction of all workers that therapy with these preparations is reliably effective. It does not seem to me that the general practitioner is likely to use "cortin," particularly now that desoxycorticosterone is available, except in rare instances in the treatment of a crisis (see below).

Ascorbic Acid (Vitamin C).—There are observations indicating the participation either of vitamin C in cortical function or of cortical function in vitamin C metabolism. The state of our knowledge is still inexact but it would seem unlikely that any harm could be done, and possibly some good might accrue, from supplementing the dietary with additional ascorbic acid (see Scurvy for methods).

Therapy of Crisis.—Thorn (1944) gives 1000 to 1500 cc. of physiologic saline solution with 5 to 10 per cent of dextrose, repeating the infusion in six to twelve hours and subsequently at least once daily until the temperature is normal and the patient is taking fluids and eating well. He considers that morphine is contraindicated and that all unnecessary examinations should be deferred at this period. Twenty-five cubic centimeters of cortin are added to the first intravenous infusion and another 10 cc. are given subcutaneously, repeating the latter at two-to four-hour intervals until fever subsides, then at four to eight hours until the patient is eating well. Twenty milligrams of desoxycorticosterone acetate are injected intramuscularly immediately and thereafter 5 to 10 mg. once daily depending on blood pressure, quantity of saline solution which has been administered, appearance of excessive fluid retention and other factors. One cubic centimeter of epinephrine in oil injected intramuscularly, or half the amount in aqueous solution, is considered indicated if the systolic blood pressure falls below 90 mm., blood pressure determinations being made at one- to two-hour intervals day and night. A fall in blood pressure without signs of excessive sodium chloride and water retention is looked upon as definite indication for increasing the infusions and giving additional desoxycorticosterone acetate intramuscularly. Fall in blood pressure in the presence of excessive sodium chloride and water retention is considered definite indication for a reduction of the number of infusions, for discontinuing the desoxycorticosterone acetate, and for increasing the quantity of cortin, *i.e.*, 10 cc. every hour. At this time a transfusion of blood plasma is seriously considered.

DIABETES MELLITUS

The islands of Langerhans in the pancreas normally secrete a hormone, insulin, which promotes in some complex way the oxidation of dextrose and its conversion into glycogen and the deposition of this glycogen in the liver and the muscles; in addition it in some way influences the conversion of pro-

tein and fat into sugar. When the production of insulin is markedly decreased, there is an increase in blood sugar above the normal amount, sugar appears in the urine, and we say that the individual has diabetes mellitus. The principal symptoms are a marked increase in the amount of water drunk and food eaten, frequency of urination and oftentimes polyuria, and a loss in weight and strength which the patient finds difficulty in reconciling with his great increase in food intake—*plus sugar in the urine.* This latter symptom, or rather laboratory finding, is the most important of all, for it cannot be gainsaid that it is a sound diagnostic principle to regard every person with sugar in the urine as a diabetic until he is proved not to be; *i.e.*, until it is shown that the glycosuria is not one of the following types, reviewed by Bock in 1944: (*a*) rare true renal glycosuria (normal blood sugar but low renal threshold for sugar); (*b*) physiologic lactosuria during lactation; (*c*) fairly frequent mild glycosuria of pregnancy which disappears after parturition; (*d*) that glycosuria sometimes manifest during acute infectious diseases, hyperthyroidism, hyperpituitarism, malignancy, traumatic injury to the brain, carbon monoxide poisoning, general anesthesia, the use of xanthine diuretics, strychnine or morphine; (*e*) "alimentary" glycosuria following carbohydrate stuffing in some individuals, or after full feeding of a patient who has been starving; (*f*) the rare condition, of familial tendency and apparently limited to individuals of at least distinct Jewish lineage, characterized by constant presence in the urine of small quantities of pentose (Edelman and Reiner, 1943, reported a case of coexistent pentosuria and diabetes mellitus), which may perhaps normally appear also after a debauch of plums, cherries, grapes, or prunes; (*g*) the rare benign congenital error of carbohydrate metabolism known as essential fructosuria (levulosuria); (*h*) emotional glycosuria of a transitory nature.

When there is lack of insulin in the tissues—that is to say, in a case of diabetes—not only is carbohydrate oxidation disturbed but there is also interference with fat catabolism and increased excretion of nitrogen as a result of protein destruction to augment the supply of dextrose. The result of the disturbance in fat metabolism is that β-oxybutyric acid and its derivatives collect in the tissues and a state of acidosis (more correctly, ketosis) is set up which, if allowed to progress, culminates in the most dreaded symptom of all—coma. The presence of these bodies is easily detectable in the urine, but the other symptoms of mild acidosis are too vague to be described here. Indeed, of coma itself the prodromal symptoms are very elusive. Any of the following should arouse suspicion: loss of appetite; nausea and vomiting; diffuse abdominal pain, tenderness and spasm; restlessness, excitement, unusual fatigue, dizziness, ringing in the ears, and disturbances in breathing. The "coma" itself may range from a state of great drowsiness to deep unconsciousness from which the patient cannot be aroused. There is usually Kussmaul breathing, acetone breath, the appearances of marked dehydration, leukocytosis, a low plasma carbon dioxide-combining power but a high blood content in sugar and ketone acids, a comparatively low percentage of sugar, salt and nitrogen in the urine but a high concentration of acetone and diacetic acid, poor peripheral circulation, and often a peculiar softness of the eyeball not seen in other types of coma. When there are accompanying signs of renal failure these almost invariably disappear without sequelae if the attack of coma is survived.

Extremely interesting experimental studies in recent years are indicating that disturbance in the production of the internal secretion of the pancreas,

which is looked upon as underlying diabetes, may be in part a mere reflection of the overactivity of other endocrine glands, especially the hypophysis, thyroid and adrenals, or that there may be "antihormones" which must be reckoned with in future investigations of the nature of insulin's action. But these things have not as yet affected practical therapy.

The most frequent time of onset is in the early fifties, but the disease may appear at any age. Formerly diabetes in children, in young adults and in pregnant women was felt to have an almost hopeless prognosis, but insulin has entirely changed the status of these patients. The disease is encountered in all races; incidence is higher in Hebrews than in Gentiles, and in Hebrews female patients outnumbered males 2:1 in Rudy and Keeler's (1939) study; in the Negro, females outnumbered males 4:1 in Altschul and Nathan's (1942) study; the incidence is apparently higher too in the Irish, and in the rich than in the poor. The hereditary transmission of a "tendency" for development of diabetes, as well as the contention that obesity and probably also thyrotoxicosis predispose, may tentatively be considered proved; indeed Newburgh and Conn (1939–1942) reported a group of individuals whose glycosuria and hyperglycemia disappeared upon correction of their obesity alone. The most thorough study of the cause of death in diabetes that has come to my attention in recent years is that of Robbins and Tucker (1944), who found in an analysis of 307 autopsies on diabetic patients at the Boston City Hospital that the diabetic lives as long as the nondiabetic nowadays but that there are certain hazards that he is seemingly more likely to encounter, namely, coronary occlusion, peripheral vascular disease, infections of the extremities and acute pyelonephritis. The frequency with which chronic gallbladder disease, tuberculosis and advanced arteriosclerosis are diagnosed among diabetics is also certainly worth remarking. Siegel and Allen (1941) called attention to the occurrence among middle-aged, mild hypertensive diabetics of a clinical syndrome closely simulating chronic glomerulonephritis, with a nephrotic phase and often terminating in renal failure. Despite the fact that the literature is replete with reports of "acute" cases, it is still the consensus that in the majority of instances the onset is gradual. Diabetes incidence is trending upward throughout the world; indeed Blotner and Hyde (1943), in studies which Joslin (1944) considers of great importance, found the incidence among 45,650 consecutive selectees for the armed forces to be more than three times that for a similar age-group ascertained by the U.S.P.H.S. through a house-to-house canvass in 1935–1936. In civilized lands, diabetes mortality is decreasing in childhood and early adulthood, but it is increasing in late middle and old age, especially among women.

Attempts to classify cases of diabetes as mild, moderate, or severe upon the degree of any of the symptoms, and especially with regard to the amount of sugar in the urine or in the blood at the first examination, are usually unsuccessful for two reasons: first, because the patient often presents himself either after a food debauch, and consequently with a high glycosuria, or after a period of severe abstinence designed to impress the new physician with his earnestness as a patient; and second, because it is by no means infrequent for patients with an astonishingly low carbohydrate tolerance to respond remarkably well to treatment that is properly planned and executed. That most cases of diabetes are actually mild is a truth that is becoming increasingly apparent—which is, however, by no means the same thing as saying that the disease is not a serious one even in the mildest cases.

In the Sanskrit manuscript of Suśruta (fifth century, A.D.) the principal symptoms of this disease are noted and the entity is given a name which translates into "honey urine." The observations were several times confirmed by Christian and Mohammedan writers of the medieval period, but it was only in 1776 that Matthew Dobson proved that the sweetness of blood and urine was actually due to the presence of sugar.

THE DIETETIC PROBLEM IN DIABETES TREATMENT

The diabetic differs from a normal individual in that, because of the shortage of insulin in the blood, the tissues cannot utilize to the full the principal source of calories in the food, *i.e.*, the carbohydrates. The caloric deficit cannot be made up to a very great extent by increasing the amount of protein in the diet for the following reasons: (*a*) the specific dynamic action of protein is so high that, in employing it in sufficient amount to overcome appreciably the shortage in carbohydrate, the total caloric need would be so much increased that the dilemma would become more rather than less trying; (*b*) the amount of protein that would have to be eaten would be so great that the diet would be entirely unpalatable for more than a very short period; (*c*) and finally, this protein in the course of catabolism would yield 58 per cent of itself in the form of carbohydrate to tissues that are already surfeited with carbohydrate which they are unable to use. As compared with protein, fat has three advantages: first, each gram yields 9 rather than 4 calories; second, its specific dynamic action is lower than that of protein, thus enabling it to be used without so greatly increasing the total caloric need; and third, only 10 per cent of it is converted into carbohydrate in the course of catabolism. But its disadvantages are unfortunately grave. Of the two disadvantages of fat the least important, but by no means *un*important, one is the fact that fat, in large enough amount to raise the total calories to a point approaching satisfaction, is very repugnant to the gastro-intestinal tract and often provokes a most undesirable state of indigestion. But the chief disadvantage is that fat is improperly metabolized in diabetes. We used to believe that this was because fat needs carbohydrate for its proper oxidation, but now the work of Stadie (1940) and others has made that position untenable; however, though it is no longer permissible to say that "fat burns in the fire of carbohydrate," we do know that beyond a certain level in the diabetic fat metabolism is incomplete and that part of the fat catabolized is excreted in the form of ketone bodies. These ketone bodies are poisonous in that they attach themselves to basic radicals from which they displace the weaker carbonic acid, thus bringing about the presence of carbon dioxide in excess in the blood. If this goes on in only a small way, surplus carbon dioxide is eliminated through the lungs and some of the ketone bodies are passed out through the kidneys, but if protein is being kept as high as is thought to be necessary for the body needs, and the carbohydrate tolerance is very low, then the attempt completely to make up the caloric deficit with fat will finally and inevitably lead to acidosis and coma.

Prior to the advent of insulin for parenteral use in 1922, both horns of this dilemma were grasped firmly, if ineffectually, by simply starving the patient. If his carbohydrate tolerance was very low and he could not bear large amounts of protein and fat for the reasons which have just been presented, he was merely placed on that amount of carbohydrate, protein and fat which he *could* utilize—and thus was kept living though hardly alive. The condition of these undernourished patients was, in severe cases, deplorable in the extreme, and

they usually died in a short time, either directly or indirectly from undernutrition or from coma following the breaking of an intolerable dietary regimen. When insulin arrived on the scene its use was at first merely engrafted upon the above treatment, *i.e.*, the "tolerance" of the patient was determined by building up the carbohydrate after starvation to the amount he could utilize and then insulin was added to enable him to take a little carbohydrate for a little more comfort. In those days the apportioning of the carbohydrate (C), protein (P), and fat (F) fractions of the diet was dictated by the formula $F = 2C + \frac{1}{2}P$, by which Woodyatt had made clinically available the laboratory researches of Shaffer. But as time went on and experience increased, the following clinical observations made it apparent that the principle needed considerable revision: (1) Patients so strictly managed were always perilously close to ketosis and therefore at all times in a more or less potentially dangerous condition. (2) Patients who did not take the thing too seriously and now and then moderately indulged in excess carbohydrate often escaped acetonuria despite the development of glycosuria. (3) With a little sugar in the urine the patient usually felt better. (4) By utilizing to the fullest extent the pancreas-resting function of insulin, carbohydrate could be raised and fat lowered out of all relation to the formula with a tremendous increase in both safety and well-being of the patient. It is nowadays the practically universal custom to carry patients on a dietary that is high in carbohydrates and low in fats, under which regimen it is found that insulin takes care of astonishingly larger amounts of carbohydrate than was thought possible in an earlier period. These high carbohydrate-low fat diets are more palatable, they are cheaper and easier to prepare, they are more nearly normal, and they maintain the patient in a stronger condition—a stoker or plowman *can* stoke or plow—and feeling thoroughly at ease. Insulin reactions are fewer and less severe. It has also been remarked that upon the new type of therapy patients who formerly had persistently high blood sugars are seen less frequently and that the refractory diabetic responds more "normally." There is some evidence also that the new diets may be effective in reducing the incidence of arteriosclerosis and also in lowering hypertension, but it is very difficult to be certain about these things.

BARACH'S SIMPLE METHOD OF DIETARY COMPUTATION

(*All of the Tables discussed below are at the end of the article*)

Diabetic Table A.—This provides maintenance diets for males and is based upon the maximum longevity tables of the Metropolitan Statistical Bureau. It takes into account the patient's height, his body build and the extent to which he is physically active. The protein portion of the diet varies between 0.75 and 1.0 Gm. per kilo. The total fat allowance is determined by the very important fact that the dietitian cannot make up a satisfactory daily menu for the average American patient on less than 80 to 90 Gm. per day, which allows some milk, butter and fat for cooking (the very low fat diets employed by some physicians include mineral oil and substitutes which the patient discards as soon as he escapes from the hospital). After the protein and fat are provided the remaining calories are supplied by carbohydrates. If the indication arises when using this table, one may increase or reduce the diet 5, 10, or 15 per cent by adding or subtracting such amounts to or from any one of the daily allowances. If there is acetone and diacetic acid *without* glycosuria, too

little carbohydrate is being given, and both additional carbohydrate and insulin are necessary. Barach (1942), reviewing a series of about 2000 cases, found that 35 per cent of his patients required insulin and 65 per cent did not. If there is acetone and diacetic acid *with* glycosuria, fat and protein must be reduced and carbohydrate and insulin are imperatively needed.

It will be observed that in employing this table it is not necessary to do any calculating at all; you simply locate your patient as to height and body build and then read off his calorie and protein, fat and carbohydrate requirements for the day.

Diabetic Table B.—This is the same as Table A except that it takes into account the somewhat different weights and nutritional requirements of women.

Diabetic Table C.—This provides maintenance diets for growing children. It takes into account the differences in weight between girls and boys and the necessary alterations when the growth rate slows.

Diabetic Table D.—This table shows the manner of distributing the carbohydrate portion of the diet throughout the three meals of the day. If, for example, the patient is a woman whose height is 5 feet 9 inches and body build large, reference to Table B will have shown that she is to be allowed 240 Gm. of carbohydrate, 80 Gm. of protein and 95 Gm. of fat daily. One then turns to this present Table D and finds, in the column designated by the check mark (√), that the patient may take 365 Gm. of 6 per cent fruit, 40 Gm. of cereal (dry weight) and 60 Gm. of white bread for breakfast; 190 Gm. 20 per cent vegetable, 200 Gm. 6 per cent fruit and 60 Gm. bread for lunch; 180 Gm. 20 per cent vegetable, 200 Gm. 6 per cent vegetable, 200 Gm. 6 per cent fruit and 40 Gm. bread for dinner in the evening. In obtaining the carbohydrate portion she will also have obtained 20 Gm. protein (the lowest figure in the 240 Gm. column); this is to be taken account of in the use of the next table.

Diabetic Table E.—This provides the protein and fat portions of the diet. Our supposititious patient, described above, is to be allowed 80 Gm. of protein, but in taking care of the carbohydrate allowance above, 20 Gm. of protein were incidentally obtained; one therefore subtracts 20 from 80 and allows the patient 60 Gm. of protein, which, as designated by the check mark in this present Table (√), will permit her to have 100 Gm. of meat for each of the three meals. It will be noted that in taking this 60 Gm. of protein she also acquires incidentally 60 Gm. of fat; this fact will be taken account of in the next table.

Diabetic Table F.—This table provides the additional fat portion of the diet. Our supposititious patient is to have 95 Gm. of fat, but in acquiring her protein she also acquired 60 Gm. of fat incidentally; one therefore subtracts 60 from 95 and allows her 35 Gm. of fat, which, as indicated by the check mark (√) in this present Table, will permit the taking of 12 Gm. of butter at breakfast, 14 Gm. of butter or mayonnaise for lunch and 15 Gm. of butter or mayonnaise for dinner—in short, this additional fat portion is to be distributed more or less equally between the three meals.

Diabetic Table G.—This lists carbohydrate exchanges which provide considerable opportunity for introducing variety into the menu; the table is very easily employed by following the simple instructions which accompany it.

Diabetic Table H.—This is a necessary table of percentage fruits and vegetables.

Diabetic Table I.—This is a table of meat exchanges and, as in the case of the carbohydrate table, is very easily employed by following the simple instructions.

Diabetic Table J.—This is simply a table of supplementary information on foods, designed to supply the answer to numerous frequently asked questions.

THE INSULINS

There are now available four principal forms of insulin and I shall describe the use of each below, but the reader must bear in mind that their insulin value is precisely alike, *i.e.*, a unit of insulin is always just a unit of insulin, no more and no less, whether it is used in the form of regular insulin, crystalline zinc insulin, protamine zinc insulin, or globin zinc insulin. These insulins vary in the rate at which they become absorbed and available in the body, but unit for unit they promote identical degrees of metabolic regulation. The frequently employed practice of giving one unit for each 2 Gm. dextrose output in the urine seemed to find support in Miller and Allen's (1939) attempted mathematical evaluation; still it is well to bear in mind that there are many variables which can affect the relationship, and to employ this rule of 1 to 2 as only a crude approximation. One can determine, again roughly, the amount of dextrose in a given specimen of urine from the color reaction obtained from the test with Benedict solution: red corresponds to 4 per cent or more, orange to 3 per cent, yellow-green to 2 per cent, green to 1 per cent.

Insulin is deeply injected subcutaneously, the site being changed so frequently that the same spot is not used more often than once a month. It is well to have patients map out all available sites in order to avoid duplications. The sites usually used are the anterior aspects of the legs, the deltoid and triceps regions of the arms, the upper portions of the buttocks and the abdominal wall. When, as may occasionally happen, it is necessary to add 0.1 cc. of 2 per cent procaine hydrochloride solution to the insulin, epinephrine should not be used, as is the usual custom with procaine.

Regular Insulin and Crystalline Zinc Insulin.—These are the fast acting insulins, regular insulin being the one originally introduced and crystalline zinc insulin being the currently employed preparation of the synthetic drug, the two being used interchangeably unit for unit. They begin to exert their effect immediately upon injection and have completed their action in a few hours. If a case is so mild that it may be controlled with only a single dose of one of these rapidly acting insulins, many practitioners prefer to have this dose taken twenty to forty minutes before breakfast; however, most patients will require another dose before dinner in the evening, many a dose also before lunch, and in some instances even a fourth injection must be given. The practical advantage in having the insulin injected before rather than after the meal is that the nervous type of individual, always fearful lest something will prevent him getting his meal at the proper interval after injection, is much more at ease when all his senses and the weight of the family as witnesses combine to assure him that he is actually replete with food when the insulin begins its work.

In the day-to-day treatment of diabetes these two insulins are not much employed nowadays, being reserved principally for use in diabetic emergencies and to supplement protamine zinc insulin.

Protamine Zinc Insulin.—A good index of the extent to which protamine zinc insulin has replaced regular insulin is obtained in the statement made by

Joslin *et al.*, as long ago as 1940, that practically all of their patients in the great George F. Baker Clinic of the New England Deaconess Hospital in Boston, who require insulin, are obtaining it in this form. The outstanding advantages of this new agent are the following: (*a*) Only one injection need be given per day because the drug has a remarkable constancy of action; *i.e.*, when given in the day-by-day treatment of diabetes it furnishes a continuous and relatively even supply of insulin from the subcutaneous depots. Once fully established, the action, as shown by Ricketts (1941), is maximal at all times, thus enabling the patient to take his injections at whatever time is most convenient, provided they are spaced twenty-four hours apart. (*b*) The blood sugar level during fasting is set at a certain level by this drug, the height depending upon the dose. The blood sugar is pushed above this level by food during the day and gradually returns to it when the patient is without food during the night; nocturnal hypoglycemia does not indicate a greater action during the night but merely that the dose used is setting the basic level too low. (*c*) The patient's nervous tension is greatly lessened because meals need not be taken absolutely on schedule. (*d*) There is a general impression that ketonuria, diabetic coma, and gangrene and infection of the lower extremities occur less frequently since protamine zinc insulin has become generally used.

Joslin (1944) states that 80 per cent of his adult diabetics are adequately controlled with protamine zinc insulin alone. However, an amount of protamine zinc insulin which will keep the patient's urine sugar-free throughout the day places him upon a hypoglycemic level at various times throughout the twenty-four hours and makes him extremely liable to severe hypoglycemic reactions during the early hours of the morning. To obviate this disadvantage the thing to do is supply additional carbohydrate at frequent intervals throughout the day and especially late at night. Several plans have been adopted, as follows:

Late Protein.—Pollack and Dolger (1938) reported good success by availing themselves of the fact that protein slowly yields about 50 per cent of itself as carbohydrate; they simply instructed their patients, after a preliminary careful quantitative study in 40 individuals, to take half or more of their daily protein allowance at the evening meal in order to buffer the tendency toward dangerous degrees of hypoglycemia during the night.

Eating Between Meals.—The plan of Collens and Boas (1939) stressed what they called "intercibal feedings," *i.e.*, the taking of food at 10 A.M., at 3 or 4 P.M. and again very late at night, this in addition to the usual three meals. The plan, with regard to distribution of carbohydrate, follows:

Time	Meal	Per Cent of Total Carbohydrate in 24 Hours
8 A.M.	Breakfast	25
10 A.M.	Intercibal feeding	7
12 noon	Lunch	25
3–4 P.M.	Intercibal feeding	7
6 P.M. (later, if possible)	Dinner	20
11–12 P.M.	Postcibal feeding	15

These intercibal feedings are not more than snacks such as a small amount of fruit juice, though the last one at night should also contain some protein from which carbohydrate will become slowly available.

The Four-Meal Day.—Margolis and Eisenstein (1940) recorded results with

which they were highly pleased, their only departure consisting in replanning the patient's schedule on a four-meal basis. The caloric division was as follows: $\frac{1}{5}$ of the total caloric intake at 8 A.M., $\frac{1}{5}$ at noon, $\frac{2}{5}$ at 5 P.M., $\frac{1}{5}$ at 9:30 P.M. In some instances the last meal has contained the $\frac{2}{5}$ portion if necessary. They reported several cases in which single morning doses of 50 to 80 units of protamine were handled on this regime without reactions and without the supplementary employment of regular insulin. This method has been widely adopted with apparently rather general satisfaction in mild or only moderately severe cases.

Relative Disregard of Sugar.—This plan of treatment involves a very wide departure from previously accepted practice in that it does not look upon absence of glycosuria and a constantly normal level of blood sugar as the true gauge of successful treatment. It is based rather on the assumption that if a patient receiving one dose of protamine zinc insulin daily can take a high carbohydrate-low fat diet of the type nowadays commonly employed in diabetics, maintain his weight, be in nitrogen equilibrium (*i.e.*, not have tissue proteins consumed during the night to obtain carbohydrate), excrete no ketone bodies in the urine, and be absolutely free from symptoms, it does not greatly matter if he has a more or less constant hyperglycemia and even glycosuria. The foremost exponent of a therapy based upon this premise is Tolstoi, who, at the time of his first comprehensive report in 1940, had treated 84 patients without an attempt to "desugarize." In 1944, Tolstoi reported that the treatment had become routine at his clinic at the New York Hospital. When a patient presents symptoms as well as a glycosuria he is put upon a carbohydrate diet and started off with 15 to 20 units of protamine zinc insulin. If the patient remains symptom-free, maintains his weight or gains in weight, and has no acetone in the urine, on the diet and this amount of insulin, and if furthermore he is socially and economically useful, his treatment is considered satisfactory regardless of the amount of glycosuria he may have. If, however, in addition to his glycosuria he is losing weight on an adequate diet, or in addition to the glycosuria has such symptoms as thirst, frequency, or weakness, the dosage of protamine zinc insulin is increased by 5 units every three days until symptoms disappear and the weight has leveled off at the optimum for the individual. Occasionally, because of a slight cold or without any obvious cause, a slight trace of acetone will appear in the urine. This patient is not hospitalized, particularly if he has been trained, but instead he is told to take salty broths freely, and is given $7\frac{1}{2}$ grains (0.5 Gm.) tablets of sodium chloride, 2 tablets to be taken every two or three hours, following each with a glass of water. He is told to test his urine at each voiding and as long as acetone continues to be positive to supplement the basic daily dose of protamine with regular insulin. If the test for sugar is red or yellow he is to inject 25 units of insulin, if green to yellow 15 units, and if blue or negative he is to take the juice of an orange. This routine is employed *only* if and when acetone appears. Of course, if an infection is severe, or if the patient has not been trained, he is hospitalized when ketosis supervenes. In Tolstoi's scheme little attention is paid to the blood sugar from a therapeutic standpoint and glycosuria is disregarded. He does emphasize, however, the importance of maintaining weight, freedom from symptoms and absence of ketosis; and he also warns the patient of the seriousness of any infection or gastric upset and of the importance of never reducing or discontinuing the use of insulin unless so ordered.

Tolstoi has had patients on this type of treatment for three to five years

and has not found any clinical support in his experience for the traditional dicta that hyperglycemia and glycosuria contribute to numerous complications of which infections, atherosclerosis and coma are the most dreaded. It is significant that at about the same time the work of Tolstoi, who is at Cornell, began to appear, Bridge and Winter (1939) had concluded from their studies of the effect of insulin on diabetics, at Johns Hopkins, that neither the value for blood sugar nor the degree of glycosuria is an adequate criterion for the regulation of diabetes. Tolstoi's unorthodox type of treatment has of course met much opposition, but I feel that we will hear much more of it nevertheless, for all his patients were of the clinic type, at work and glad to be relieved of careful dietary measurements.

Protamine Plus Regular (or Crystalline Zinc) Insulin.—Most patients with mild diabetes requiring no more than 30 or at most 40 units of protamine zinc insulin may usually inject this amount all in one dose before breakfast—the time which seems most convenient for the majority of individuals—and obtain satisfactory control without hypoglycemia as a constant threat. But when larger doses are required it usually happens that if sufficient is given before breakfast to keep the blood sugar normal throughout the day the patient is extremely liable to hypoglycemic reactions in the early hours of the morning. Of course one could give a smaller amount of protamine and then inject some regular insulin before each meal to take care of the postprandial rise in blood sugar, but in such a practice it is difficult to see that anything is gained by using a protamine at all. Most men compromise by giving an amount of protamine calculated to keep the blood sugar normal after it begins to become operative and combining with it in the morning an injection of a small amount of insulin to take care of the rise after breakfast before protamine effect has fully developed. It has not been possible to devise a ratio of the two insulins which would be satisfactory in all cases, but ample experience has shown that mixtures in equal parts behave essentially as protamine zinc insulin alone, whereas the activity of a combination of three parts of insulin to one part of protamine zinc insulin is too much like that of insulin alone. The statement made by Peck in 1943 seems still to hold, namely, that the most generally useful extemporaneous mixtures are in the ratio of three to two or two to one parts of insulin to protamine zinc insulin. The mixtures must be extemporaneously made by the patient, which can be easily done if the following directions (Peck 1943) are implicitly followed: (*a*) inject a volume of air equal to the dose into the top of the vial of protamine zinc insulin, and withdraw the empty syringe and needle; (*b*) inject air and withdraw the proper dose of insulin from the vial in the usual manner; (*c*) invert the vial of protamine zinc insulin several times and withdraw the dose into the syringe containing the insulin; (*d*) holding the syringe with needle upright, draw air bubble into syringe, invert and roll the bubble through to mix. Of course, the performance of even these uncomplicated procedures is beyond the intelligence of many individuals; in such cases the two insulins have simply to be injected separately.

MacBryde and Roberts (1943) are working with a specially modified protamine zinc insulin with 75 per cent slow and 25 per cent rapid effect, which is said to be accomplished by the admixture of equal parts of protamine zinc and regular insulin at *p*H 7.2. It will be very interesting to watch these experiments; the product is not yet commercially available to my knowledge.

Globin Zinc Insulin.—The observations of Andrews and Groat (1940), Duncan and Barnes (1941), Bailey and Marble (1942), Lawrence (1943) and

Mosenthal (1944) indicate that the effect of globin zinc insulin upon the blood sugar usually lasts from twelve to sixteen hours and occasionally as long as twenty-four hours. It therefore combines some of the rapid action of regular or crystalline insulin with the more prolonged action of protamine zinc insulin. Mosenthal, in common with others, finds it necessary when using this preparation to give an extra feeding between 3:30 and 4:00 P.M. to check the low blood sugar developing at that time; Marks (1940), however, felt that he had successfully eliminated this intermediate meal by distributing the carbohydrates throughout the day as follows: 20 per cent at breakfast, 40 to 50 per cent at lunch and 30 to 40 per cent at dinner in the evening. Globin zinc insulin has achieved nothing like the popularity of protamine zinc insulin, but Mosenthal (1944), summarizing his experiences with it, says he finds it reassuring to have it as a "second string to our bow."

Globin zinc insulin is measured and injected like the other insulins but it should not be combined in the same syringe with protamine zinc insulin. Mixtures of globin zinc insulin and regular or crystalline zinc insulin are illogical and have not been attempted.

Other Insulins.—It seems to me that none of the other insulins, such as hexamine insulin and histone zinc insulin, justify description in the book as yet.

Systemic (Hypoglycemic) Reaction.—When an overdose of insulin has been taken the patient experiences a feeling of general muscular weakness, "hollowness" in the stomach accompanied by great hunger, subjective and objective trembling, paresthesias, restlessness and temporary loss of memory, sweating and pallor or flushing of the face, increased pulse rate, headache, nausea and vomiting. If regular or crystalline zinc insulin has been taken these symptoms may be experienced very suddenly or they may come on gradually during the course of a quarter-hour; if protamine zinc insulin has been injected the onset may be very much slower. In the more severe reactions the face assumes a masklike expression, there is diplopia and complete disorientation, and the patient may become unconscious and show a profound fall in temperature and blood pressure; epileptiform convulsions are also seen in some instances; likewise a wide variety of behavioristic and mental changes foreign to the patient's normal personality may be manifested. Deaths have been reported but they are rare. However, there does exist a possibility of serious and permanent cerebral damage; Murphy and Purtell (1943) summarized 26 such cases from the literature and added one of their own. Other things being equal, the thin, frail, feeble patient is the most likely to develop reactions. Delayed absorption of food can certainly lead to hypoglycemic shock in a patient who has taken insulin before eating; since emotional disturbance is the chief cause of such delay, the advisability of maintaining as perfect emotional balance as possible for diabetics, especially at mealtimes, has been fully established.

The insulin reaction is commonly ascribed to a sudden hypoglycemia, but it is well not to overlook the fact that some other mechanism may also be involved since not all individuals in whom the blood sugar falls very considerably experience such a reaction; indeed, John has described such reactions with a normal or increased percentage of blood sugar. Foshay believes that not so much the hypoglycemia *per se* as the relatively greater dextrose impoverishment within the cell is to be held accountable. Müller and Petersen look upon an acute disturbance of the autonomic nervous system as the cause of the shock, of which hypoglycemia is only one of many symptoms. Unquestionably

a very few of the reactions are allergic in nature, for they follow the use of one brand of insulin but not the use of another.

Dextrose.—Any carbohydrate out of which glucose (dextrose) may be quickly formed in the body is the antidote. Orange juice is usually taken by the patient at home and it acts very well. One or 2 lumps of sugar, depending upon the size of the individual, quickly dissolved in the mouth are also effective in overcoming the symptoms. If the patient is unable to swallow easily, honey or corn syrup may be used. In any case, after a rest, the dose should be repeated.

Intravenous injection of dextrose may be made if the patient is unconscious; also it must sometimes be resorted to in patients who have not lost consciousness but in whom the hypoglycemia seems to be accompanied by a depression in the absorptive power of the intestinal mucous membrane (or should the failure to respond to the oral administration of dextrose be ascribed to acute peristaltic lapse?). Not more than 25 Gm. should be given in this way in a solution of 5 to 50 per cent strength—500 cc. of 5 per cent, 250 cc. of 10 per cent, 125 cc. of 20 per cent, 50 cc. of 50 per cent; usually smaller amounts suffice, but occasionally larger quantities need to be given. Joslin *et al.* (1940) said that in severe cases in which consciousness does not return within an hour it would probably be advisable to employ constant intravenous administration of 10 per cent dextrose solution to keep the blood sugar level at approximately 200 mg. per 100 cc.

The intracardiac injection of dextrose has been reported in one case by Imerman: "The pulse was fast failing and the patient was moribund. Because of difficulty experienced previously in entering the veins of this patient, it was not deemed wise to attempt to do so now, as any further delay might be fatal. An intracardiac injection was decided on as the very last resort. This was accordingly done by means of the sterile syringe and the lumbar puncture needle (both of which, together with sterile glucose solution, happened to be at hand), and 10 cc. of sterile dextrose was injected. At the end of two minutes, the patient had recovered consciousness." As soon as possible, an additional 80 cc. of the 20 per cent solution was introduced after a vein had been surgically exposed; immediate recovery was complete.

Protein.—Protein, since 58 per cent of it is convertible into carbohydrate, may also serve as antidote; therefore, in the absence of carbohydrate food, the patient should quickly eat a large amount of some food high in protein content. However, Sherrill states that "though hypoglycemia may be prevented by sufficiently large quantities of protein, this influence is surprisingly feeble and by no means proportional to the theoretical value."

Epinephrine or Pituitrin.—Epinephrine (adrenalin) is effective in combating the insulin reaction, but in undernourished individuals carbohydrate should be given with it; indeed, there would seem to be little reason to use this drug when carbohydrate is at hand for in all cases its action is quite transient and must be reinforced by the subsequent taking of glucose. The epinephrine dose is 0.5 cc. in the child, and 1 cc. in the adult, of the 1:1000 solution, given intramuscularly. Graham (1934) reported the effective use of pituitrin in 1-cc. injection.

Calcium.—Greiff (1931) reported 2 cases in which the giving of $1\frac{1}{4}$ ounces (40 Gm.) of calcium gluconate daily, either by mouth or in enema, was effective in overcoming insulin hypersensitivity so that a daily injection of 40 units could be resumed; Atchley *et al.* employed 20 to 35 Gm. of calcium chloride.

Enforced Omission of Insulin or Food.—Under the wartime vicissitudes in bombed England consideration had to be given diabetics likely to be suddenly without either food or insulin. The advice of Lawrence (1940) may be briefly summarized as follows: (*a*) If a diabetic cannot get his usual insulin his best chance of minimizing ketosis is to continue to eat his usual carbohydrate but no fat and only a little protein; upon resuming the interrupted routine extra insulin dosage may be required to get back to the old status. (*b*) If a diabetic's insulin supplies are running short it would probably be fairly safe for a few days to cut dosage in half and continue the usual diet but with elimination of fat. (*c*) If insulin is available but carbohydrate food is not it is probably advisable as a general rule for the severe diabetic to take one-third to one-half his usual insulin without food, taking the usual meal and insulin as soon as food becomes available or the usual food and only a half dose of insulin if the preceding dose had been taken within six hours.

Insulin and Exercise.—Exercise exerts a very profound effect upon the diabetic. Even before the inauguration of the insulin era it was known that the mild diabetic was improved and the severe diabetic made worse by exercise. Nowadays exercise must always be taken into account in injecting insulin, for, other things being equal, the more exercise the less insulin will be needed; in some instances the taking of a usual dose of regular insulin may result in a hypoglycemic reaction if considerable exercise has preceded the injection. Many times it is possible for a golfer or an amateur gardener to eliminate a few units or an entire dose (that is if he is taking regular or crystalline zinc insulin) on the days when he has indulged his hobby. It has been noted also that children romping about in summer diabetic camps require less insulin than during the winter when they are less active. That the effect is not universal is emphasized, however, by the study of Soskin *et al.* (1934), whose 2 carefully studied patients did not show significant decreases in insulin requirements during a systematic course in physical training. Furthermore, Marble and Smith (1936) found that for exercise to exert its maximum benefit sufficient insulin must be available in the body at the time of exercise; *i.e.*, the preferable sequence for the diabetic should be insulin, exercise and breakfast rather than exercise, insulin and breakfast.

Insulin Edema.—Very few cases of insulin edema have been reported but there seems to be a clinical impression that this complication occurs not infrequently. The exact nature of the phenomenon, which is not due to impaired renal or cardiac capacity and which clears up when insulin is omitted, is not understood. Observers believe variously that insulin edema is a colloidal phenomenon; that insulin increases the hydration capacity of the tissue colloids of the body; that the alkali set free when insulin is given leads to water retention; that the explanation may lie simply in the fact that 3 Gm. of water are retained for each gram of carbohydrate stored. Leifer's patient became edematous and gained 26 pounds in ten days, then lost the edema and 12 pounds during the succeeding ten days apparently as a result of marked reduction in the salt of the diet; insulin dosage had remained practically the same. It is said that the edema can sometimes be made to disappear by dropping down with the insulin dosage and gradually building up again. If alkaline therapy is being employed it should be stopped.

Insulin Resistance.—The record of insulin-resistant cases—*i.e.*, of those who either do not respond at all, or temporarily or gradually lose their ability to respond—is certainly being added to as the years go on, but considering

the enormous number of individuals the world over who are taking the drug, one must say that this phenomenon of insulin resistance is of very rare occurrence. A few typical cases may be instanced: Taussig's case was given as much as 1100 units in one day without becoming sugar-free; after several months, however, the response to insulin showed considerable improvement. Lawrence's nineteen-year-old patient required 400 units per day to reduce his blood sugar to normal and to keep him sugar-free; the patient of Mohler and Goldburgh suddenly lost his responsiveness and died of diabetes after forty days of 437 units daily insulin dosage; upon the other hand, the patient of Karr *et al.*, in whom over 600 units daily did not keep the blood sugar under 200 mg., suddenly lost her resistance following the injection of a foreign protein (the serum of a rabbit that had been sensitized to a mixture of the patient's serum and insulin). In the patient of Martin *et al.* the precipitating factor was apparently an allergic reaction to protamine zinc insulin, after which response to insulin was lost; there was also apparently an allergic factor in Hart and Vicens' case and in the case of Shepardson *et al.* (1944); Greene and Thatchers' patient was resistant to protamine zinc insulin but not to regular insulin; Wiener's patient required as much as 3250 units in twenty-four hours, but eight months later was controlled on 440 units daily. Mason and Sly describe the interesting case of an infant in whom glycosuria resistant to insulin could almost be stopped by the substitution of levulose or galactose for dextrose in the diet. Wayburn and Beckh felt that in their patient, who died after a four-month period during which he was given from 500 to 2460 units of insulin daily, there was some evidence of the presence of an insulin antagonist; Lowell felt as a result of a study of his two cases that there may occur in the serum a definite insulin neutralizing antibody. Hendry has recorded a case in which great reduction in response to insulin was corrected by the use of thyroid substance, the patient having manifested a slight hypothyroidism; but the opposite picture is more usually seen, *i.e.*, insulin resistance associated with hyperthyroidism. The possible role of suprarenal and hepatic disorders has been discussed by several authors and also the direct association of hypophyseal (pituitary) disturbance with insulin resistance. Pullen and Sodeman felt they accomplished something by irradiation of the pituitary gland in their case which was associated with probable pituitary basophilism. Some of the cases are in association with hemochromatosis, others with specific infections such as tuberculosis and syphilis, or with rheumatoid arthritis. All explanations of insulin refractoriness upon a single basis are still highly speculative. Martin *et al.* said there does not seem to be any established upper limit to the number of units of insulin which may be given. Spiegelman treated 9 diabetic women with estrogenic hormone as used in the handling of the menopause (*q.v.*) and effected a diminution in their insulin requirement, a type of therapy which conceivably could be helpful in some cases of insulin resistance.

Insulin Allergy.—Instances of insulin allergy are observed with much greater frequency than those of insulin resistance. Some of them are due to the contained animal proteins but others undoubtedly are caused by the hormone itself since skin tests to crystalline insulin are occasionally positive. The patient may apparently manifest any of the usual allergic reactions: local edema, local or general urticaria or itching rash, asthma, severe gastrointestinal symptoms, etc.; insulin resistance (see above) is also apparently associated with allergy in some instances. Insulin allergy is a very serious

matter, for if the patient's diabetes cannot be controlled by diet alone, so that the use of insulin has to be continued, his condition may become a very deplorable one. Goldner and Ricketts (1942) thought that since interrupted insulin treatment seems to predispose to allergy, the performance of skin tests might be advisable in all patients who resume insulin treatment.

Some of the cases are arrested at once, in so far as the allergic response to insulin is concerned, by changing from protamine insulin to globin insulin, or by changing brands of the drug; *i.e.*, changing from a brand prepared from beef pancreas to one prepared from pork pancreas, or *vice versa:* changing to crystalline insulin may also be all that is required. The several methods of attempted desensitization may be presented through representative experiences: (*a*) Hallermann (1930) gave 1 or 2 intracutaneous injections of 4 to 6 units of insulin and his 3 patients were able to continue use of the drug. (*b*) Collens *et al.* (1934) gave subcutaneous doses of insulin, beginning with

TABLE 15.—RAPID DESENSITIZATION WITH LILLY'S REGULAR INSULIN (BAYER)

Units.	Time.	Reaction.
1/100	9.15 A.M.	++
1/100	9.45	++
Sterile distilled water	9.47	0
1/200	10.16	+
1/200	10.46	++
1/400	11.20	++
1/1000	11.42	+
1/1000	12.20 P.M.	±
1/500	1.30	+
1/250	2.03	±
1/125	2.32	±
1/66	3.04	±
1/50	3.36	0
1/25	4.02	0
1/10	4.16	±
1/5	4.30	±
1/2	4.45	±
1	5.01	0
5 (hypodermically)	5.20	0

++ denotes wheal of at least 1 cm. with surrounding hyperemia; +, wheal of less than 3 mm. with surrounding hyperemia; ±, no wheal, faint hyperemia; 0, no reaction.

0.0001 unit and gradually increasing by doubling the dose every other day; after three months both of their patients were able to tolerate 15 units twice daily, but desensitization lasted only one month. (*c*) Bayer (1934), using Lilly's regular insulin, known to contain both beef and pork, made up to suitable dilutions with sterile distilled water, successfully desensitized an individual in eight hours, at least in so far that the patient was thereafter able to use insulin though slight local and general reactions recurred at intervals (see Table 15); Corcoran (1938), and Ulrich *et al.* (1939), reported cases rapidly desensitized in somewhat the same manner; Weitz (1943) desensitized his case in a matter of a few days by the method indicated in Table 16. (*d*) Collens *et al.* used histamine phosphate in one case, beginning with a subcutaneous injection of 0.1 mg. and repeating the injection thrice weekly with such increasing dosage that the patient received 1 mg. on the eighth injection, and continuing at this dose to complete the series of 13 injections. The reactions to the histamine itself were quite severe, both locally and constitutionally, but

apparently desensitization to insulin was accomplished, for six months later the patient was taking 15 units daily without reaction. Roth and Rynearson (1939) reported the successful use of histaminase (discussed in Hay Fever) in 1 case; they mention 11 other cases in which they obtained "varying results."

TABLE 16.—METHOD OF DESENSITIZATION (WEITZ)

Date.	Time.	Insulin units.	Reaction.	Urine.		Blood.	Adrenalin (minims).
				Sugar.	Acetone.		
10/ 3/40	11:00 A.M.	0.1	Wheal 2 sq. cm.	4+	0	306	
	11:20 A.M.	0.1	Wheal 4 sq. cm.				
	11:50 A.M.	0.2	Wheal 4 sq. cm.				
	12:20 P.M.	0.4	Wheal 6 sq. cm.				
	12:50 P.M.	0.6	Wheal 6 sq. cm. with induration				
	1:20 P.M.	0.8	Induration, slight				
	1:50 P.M.	1.2	Induration, slight				
	2:20 P.M.	1.6	Induration, moderate				
	2:50 P.M.	2.0	Induration, marked				
	6:00 P.M.	2.4	Induration, marked	+	0		
	6:30 P.M.	2.8	Induration, marked				
	7:00 P.M.	3.2	Induration, marked				
	7:30 P.M.	3.6	Urticaria, slight				
	8:00 P.M.	4.0	Urticaria, marked	4+	0		5 × 2
10/ 4/40	8:30 A.M.	4.0		4+	0	267	
	12:45 P.M.	4.0					
	5:15 P.M.	4.0	Urticaria	4+	0		5
10/ 5/40	8:00 A.M.	6.0		4+	0	254	
	12:00 noon	6.0	Urticaria, slight	4+	0		3
10/ 6/40	8:00 A.M.	4.0		4+	0		
	12:00 noon	4.0	Urticaria, slight	4+	0		3
10/ 7/40	8:00 A.M.	4.0		4+			
	5:00 P.M.	4.0	Urticaria, slight	4+			
10/ 8/40	8:00 A.M.	6.0	Negative	4+		240	
	5:00 P.M.	6.0	Negative	4+			
10/ 9/40	8:00 A.M.	8.0	Negative	3+			
	5:00 P.M.	8.0	Negative	3+			
10/10/40	8:00 A.M.	10.0	Negative	2+		188	
	5:00 P.M.	10.0	Negative	2+			
10/11/40	8:00 A.M.	10.0	Negative	Trace			
	5:00 P.M.	10.0	Negative	1+			
10/12/40	8:00 A.M.	10.0	Negative	0		124	
	5:00 P.M.	10.0	Negative	0			

A few cases of insulin allergy, be it noted, have become spontaneously desensitized. Also, there are reports of diabetes ameliorating when the patient has become allergically sensitive to insulin.

Local Reactions.—A few cases of extensive atrophy of subcutaneous fat fol-

lowing repeated insulin injections have been reported. Less extensive involvement, especially in women and children, is by no means rare—Joslin *et al.* (1940) said that this local reaction occurs in nearly 30 per cent of their diabetic children; spontaneous recovery seems usually to occur in two years but no proved method of prevention or correction has been reported. Much rarer is the development of small lipomatous growths at the site of injection. What it is that predisposes certain individuals to this reaction is also unknown.

Local reactions of an annoying nature sometimes occur with protamine zinc insulin, but the incidence of these reactions is lessened almost to the vanishing point if alcohol is not used to sterilize the injection outfit and especially if the injections are given deeply beneath the skin; it is best to pinch up the skin and then inject at right angles into the triangle thus formed.

KETOSIS AND COMA

When the ketone bodies begin to build up in the blood the kidneys excrete acids in the free form and also as ammonium salts; furthermore some of the bicarbonates of the blood are split up to yield base for neutralizing purposes, the liberated carbon dioxide being eliminated by the lungs. When these mechanisms alone fail to keep pace with the production of acids, the fixed bases begin to be called upon and the body loses sodium—since this latter step really amounts to a decrease in total salt concentration there results a state of dehydration because water is excreted to maintain isotonicity in the tissues. Hence the patient is acidotic (due to the ketone bodies in the blood), hyperpneic (the liberated carbon dioxide must be eliminated) and dehydrated (because of the sodium chloride loss). The very obvious aims of treatment, therefore, should be to put a stop to the defective metabolism of fat and utilization of carbohydrate and to replace the carbohydrate, fluid and salt that have been lost. In short, give insulin, dextrose and saline solution. It seems to me now to be the opinion of practically all the leaders in diabetes therapy that the additional routine administration of alkalis is unnecessary since it is specifically sodium that has been lost and this is being replaced in the sodium chloride solution administered—for example, Campbell *et al.* (1940) said that the policy at the Mayo Clinic is to give 250 to 500 cc. of 5 per cent sodium bicarbonate solution intravenously only in critical instances in which there has been failure of response to the above corrective and replacement therapy; Joslin *et al.* (1942) said that alkalis are not used in their clinic.

Insulin, Dextrose, Saline.—In a series of studies since 1937, it seems to me that Rabinowitch, Fowler and Bensley, of Montreal, have established the value of their type of therapy, which consists in administering all the insulin that is likely to be necessary at one time in the beginning, using both regular insulin and protamine zinc insulin, and then giving large amounts of dextrose as long as required. With increasing experience they have decided that the best insulin dosage is the following, all injections to be given as nearly simultaneously as possible: 100 units of regular insulin intravenously; 100 units of regular insulin subcutaneously, for effect which will come on after the rapid action of that given intravenously has begun to disappear; and 200 units of protamine zinc insulin subcutaneously for its well known delayed but prolonged action. Dextrose is got into the patient by any channel possible and in large amounts—the average total amount given patients in their series of 11 cases on whom very detailed data are published was about 780 Gm. in about 40 hours. The three very apparent advantages of this type of treatment are:

(*a*) the initial amount of insulin employed is large, which is in accord with all current practice; (*b*) the method of giving the insulin insures not only an immediate but a steady and prolonged action; (*c*) and the use of large amounts of carbohydrate in the presence of all this insulin not only induces rapid reduction of ketosis but permits the storage of glycogen to take place and thus lessens the likelihood of an early reversion to the ketotic state. That the dextrose is being utilized as above indicated is shown by the fact that in their series though the average blood sugar before treatment was 612 mg. per 100 cc. it was reduced to 165 mg. in an average period of five and one-half hours, and, in spite of the administration of an average of about 780 Gm. of sugar during about forty hours, the average amount in the urine was only about 52 Gm.; in short, an average of 728 Gm. was retained and utilized in the body. Another advantage of this method of treatment, not quite so obvious as the above but nevertheless very important, is that the administration of all this carbohydrate prevents hypoglycemic reactions as ketosis is overcome. In Rabinowitch's cases there have been no reactions even when the blood sugar level has fallen very low and remained there several hours, which supports the widely accepted view that the neurological manifestations of insulin hypoglycemia are not due to lowering of the sugar content of the blood but to reduction of the sugar content of the brain.

Of course this treatment is employed in conjunction with the use of large amounts of saline. Barach's (1943) method of systematizing the therapy is shown in the accompanying chart (Table 17). The distinction between mild, moderate, severe and profound cases is difficult to make and I shall certainly not attempt it here; it seems well worth repeating that Rabinowitch and his associates now prefer the highest insulin-dextrose dosage—that designated for "profound" cases in Barach's chart—as practically routine therapy in all cases. To be sure, in an occasional case additional insulin may even have to be given in the form of supplementary injections of regular insulin and sometimes saline must also be given in quantities enormously greater than shown in Barach's chart; Joslin *et al.* (1942) speak of giving as much as 100 or more units of insulin at half-hourly or hourly intervals, and they record a case in which 11,000 cc. of saline was given in the first day of treatment.

Joslin's group is practically alone in opposing the use of dextrose in the treatment of coma; the latest presentations of their views which I have seen are those of Joslin (1945) and Root (1945).

Lavage, Cleansing Enema and Warmth.—In most hospitals, lavage of the stomach is employed routinely nowadays as soon as beginning coma is diagnosed; time has shown the procedure to be of great value, for a dilated or partially filled stomach is a great handicap to one who during the succeeding twenty-four hours must grapple catch-as-catch-can with death. Ordinarily a saline cleansing enema should be given as soon as possible. Of course the patient should be kept warm by all the devices usually employed in treating a case of shock—nearly all of these patients have a subnormal temperature at the beginning of coma, and an individual with subnormal temperature is not well armed for a fight.

Circulatory Stimulation and Transfusion.—A patient not improved by judicious application of the methods discussed above is not likely to be helped by the employment of such stimulants as epinephrine, ephedrine, metrazol, coramine, caffeine, benzedrine, and so on. Joslin *et al.* (1942) say that usually one observes temporary benefits from their use but that rarely is the outcome

TABLE 17.—INSULIN-DEXTROSE-SALT SOLUTION IN DIABETIC COMA (BARACH, 1943)

Degree of coma.	Total insulin units.	Protamine subcutaneously.	Regular intravenously.	Regular subcutaneously.	Dextrose (glucose) grams.		Fluids cc. per day.
					Per hour.	Per day.	
Mild	100 to 150	50 to 75	25 to 37	25 to 37	5 to 10	100 to 200	Give 2500 cc. for every 100 lbs. of patient's body weight. 1000 cc. every 3 hours to full amount. Rate 15 to 20 cc. per minute.
Moderate	200 to 250	100 to 125	50 to 62	50 to 62	10 to 20	200 to 400	
Severe	300 to 350	150 to 200	75	75	20	300 to 400	
Profound	400 or more	200	100	100	20	300 to 400	

1. After admission, take blood for analysis. Give the three doses of insulin at once.
2. Insulin for subcutaneous use should be divided into 3 or 4 portions and injected into different sites for better absorption.
3. Glucose is given hourly as per schedule; by mouth, gavage, skin or vein.
4. Glucose by mouth may be given as pure glucose, honey or corn syrup (Karo Syrup) mixed with water or tea and flavored with lemon juice.
5. Gastric lavage, enema and external warmth when necessary.
6. Once the insulin is given, adequate glucose administration is imperative.
7. The routine is for an average patient of average body size; extraordinary cases require individual adjustments.

changed thereby. Both Joslin's group and Schecter *et al.* (1941) favor the transfusion of whole blood or plasma where there is definite evidence of peripheral circulatory failure.

TREATMENT OF COMPLICATIONS

Intercurrent Infection.—It is well known that an acute intercurrent infection makes a diabetic worse, but it does not seem to make him permanently worse. Lawrence and McCance have suggested that the harmful effect of an infection is to be explained by the neutralization of the power of the insulin through stimulation of the thyroid and suprarenal glands, but there is likely more to the matter than simply this; for example, the theoretical possibilities of increased destruction of insulin as well as decreased production of it in the pancreas, or an interference with glycogen storage in muscles and liver; furthermore, Rabinowitch suggests that an insulin-destroying enzyme may be present during infection. If the infection is local, prompt surgical drainage is indicated (Rosenthal and Behrendt found that if fresh pus is mixed with insulin and injected into rabbits the influence of the insulin is abolished); if general, it must be recognized that the fever will cause an increase in metabolism and thus bring ketosis nearer.

Many men are still in agreement with Duncan, who said in 1939 that diabetic control can be maintained in the presence of even very severe complicating infections if the diet is divided into 6 equal feedings, spaced at four-hour intervals throughout the twenty-four hours, giving one-sixth the total insulin dosage before each feeding, and basing the amount of insulin used upon the sugar content of a specimen of urine obtained if possible before each feeding. As a practical matter, with such frequent feedings and insulin dosings, one blood sugar determination in the twenty-four hours will suffice as an index of the level. In milder infections, only 4 feedings and 4 insulin dosings may be needed, but whether the 4- or the 6-feeding routine is adopted it must be adhered to with absolute rigidity if successful control is to be expected. Duncan felt that the use of protamine zinc insulin during these acute complications is confusing and detracts from the simplicity of the program; he therefore used only regular insulin until the emergency had passed. However, Joslin *et al.* stated in 1940 that they continue protamine zinc insulin in a patient who has been taking it and supplement it at four- to six-hour intervals with regular insulin in the following dosage according to the color reaction of the urine: red, 10 units; orange, 8 units; yellow, 6 units; yellow-green, 4 units; if regular insulin is being depended upon alone, the above doses are doubled. Now that so many patients are taking either protamine alone or protamine plus regular or crystalline insulin, some such plan as that of Joslin is the one most often used in combating an intercurrent infection.

Chemotherapeutic Agents, such as the arsenicals, the sulfonamides and penicillin, may be employed in the diabetic just as in the nondiabetic. Baldwin and Root (1940), discussing urinary tract infections, also spoke of the free use of ammonium mandelate and methenamine (urotropin) and also ammonium chloride as an acidifying agent.

Tuberculosis is no longer looked upon as making prognosis hopeless; McKean *et al.* (1941) felt that mortality in cases of associated diabetes and tuberculosis parallels closely that of tuberculosis alone, an opinion supported by the rather coy statement of Foley and Andosca (1944) that they invariably give a poor prognosis in the case of a diabetic with far advanced tuberculosis

even if the diabetes is controlled. Banyai and Cadden (1944) authoritatively stated that the indications and contraindications for pulmonary collapse therapy are the same for diabetic as for nondiabetic tuberculous patients but that because of the frequency with which empyema complicates artificial pneumothorax in persons with predominantly exudative recent tuberculous lesions, the use of this measure is greatly limited for tuberculous diabetic patients.

Syphilis in association with diabetes was studied by McDaniel *et al.* (1940) in 258 patients; they concluded that syphilis does not seem to alter the type of diabetes and that it may be treated just as it would be in a nondiabetic individual.

Gastro-intestinal Disturbances.—Acute gastro-intestinal upsets are dangerous because if the patient cannot eat, or vomits what he does manage to get down, he is being deprived of carbohydrate and hence approaching closer to ketosis; insulin should not be omitted but only cut down somewhat in dosage and as careful watch as possible be kept on the levels of sugar in the blood and urine. Diarrhea is also a serious matter because it also robs the patient of food and fluids. Here again the result may be ketosis or it may be hypoglycemia; the former if the deprivation of carbohydrate causes the breakdown of body tissues, just as in the case of vomiting and inability to eat, the latter because the low state of metabolic activity of the body may render insulin relatively hyperactive. In any case the chief thing to be desired is to get food into and absorbed by the patient, covering with insulin of course; individualization of treatment is absolutely necessary.

Cardiovascular Complications.—The majority of the foremost students of diabetes agree that in arteriosclerotic, hypertensive, peripheral vascular, or coronary disturbances insulin should be employed with great caution, since sudden lowering of the blood-sugar level seems to be particularly difficult for such diabetics to combat. True anginal pain subsequent to insulin injection has been several times reported even in patients not previously having had such attacks.

Neurologic Complications.—Jordan (1936), in studying Joslin's material, found that he could separate the surprisingly large number of cases with neurologic complications into three types: (*a*) hyperglycemic, (*b*) degenerative and (*c*) neuritic. Patients in the hyperglycemic group are characterized by neuritic symptoms but with hardly any objective signs. They seem all to be relieved within a few days when the diabetes is brought under control by proper treatment. In the second and third groups there are diverse manifestations of neuropathology on a degenerative basis, with or without neuritic accompaniment, and always with arteriosclerosis. Though some of these patients improve, it seems that most do not, and I make out from the report that the particular factors at fault have not been discovered as yet. The fact stands out, however, that persistent treatment of the diabetes is indicated in all cases. In a more recent report Jordan (1943) described two cases to emphasize the fact that bone changes of atrophic nature, not ordinarily recognized as being due to diabetes, can actually be caused by the disease. Fein *et al.* (1940) described 9 cases of symmetrical peripheral neuropathy in diabetic patients, all of which responded to thiamine therapy; but Needles' (1943) 7 patients showed no improvement at all when treated with the vitamin.

Sandstead and Beams (1938) studied 13 patients with pains classified as of neuritic origin in 10 and of vascular origin in 3. The pain had persisted in spite

of treatment for the diabetes but in all instances was markedly or completely relieved upon the oral administration daily of 0.25 to 0.5 Gm. of sodium chloride per Kg. body weight, which the authors rationalized as probably indicating that ischemia was the underlying factor resulting in pain.

Eye Complications.—The principal ocular complications are: (1) transient changes in refraction, which are unimportant and apparently occur as frequently with as without insulin; (2) diabetic cataract, which seems to have decreased in incidence since insulin came into use; (3) lipemia retinalis, which is now rarely seen; (4) toxic amblyopia, which has also much decreased under careful insulin management; and (5) diabetic retinitis. This latter involvement has apparently become more prominent under the new type of treatment, possibly largely because more diabetics are living into the arteriosclerotic age. So far it has not been conclusively demonstrated whether high carbohydrate-low fat and liberal insulin therapy has served to control the progress of this serious complication. The especially interested reader will find Reese's (1935) and Wagener's (1936) reviews listed in the Bibliography; an excellent symposium on the subject appeared in the American Journal of Digestive Diseases in September, 1943.

Pruritus and Furunculosis.—These two dermatoses are frequent complications in diabetes, the former always very annoying, the latter often very serious. Their treatment is described in the chapter on skin diseases.

Vitamin Deficiencies.—A careful study of the literature of vitamin therapy in diabetes leaves the following clear impressions: (*a*) there are no vitamin deficiencies characteristically associated with diabetes; (*b*) employment of vitamins in therapy in well-controlled diabetics on adequate diets with insulin is not beneficial so far as the diabetes *per se* is concerned (the observation of Neuwahl [1943] that the employment of nicotinic acid [niacin] effects improvement in carbohydrate metabolism is interesting but requires confirmation in a large series of cases); (*c*) vitamin deficiencies occurring concomitantly with diabetes will respond to vitamin replacement therapy just as in instances not complicated by diabetes.

SURGERY IN DIABETES

Since the advent of insulin, surgical diabetic mortality has been considerably lowered, but it is still several times that of nonsurgical diabetes. Gangrene and carbuncle are the principal dealers of death. The general practitioner must be ever watchful for early signs of impaired circulation in the extremities: claudication, coldness, pain, numbness, diminished arterial pulsation, rose spots, blebs, scars. And of course he must enjoin upon his patients the necessity for utmost cleanliness of the body, particularly the feet, and the avoidance of trauma, and instant serious attention to local infections, even of the slightest. Blotner's (1936) warning that excessive smoking may predispose to diabetic gangrene should not be overlooked.

The choice of anesthetic, and the treatment of gangrene and carbuncle, are of course purely surgical matters; so also to some extent are the preoperative and postoperative care of the patient, but I think it will not be presumptuous to say two words here regarding these latter matters.

Preoperative Care.—If the patient is under good diabetic control and is coming up for an elective operation, the only preliminary alteration in surgical orders usually necessary is to have him given 6 to 10 ounces of orange juice and 10 to 20 units of insulin two hours before operation, adding 10 Gm. of

dextrose intravenously with another 5 units of insulin just before or during the operation if the carbon dioxide-combining power of the plasma is less than 40 volumes per cent. If the patient is not under diabetic control, or if the operation is of an emergency nature or complicated by infection, the treatment had better be that of acidosis with threatened coma. The diabetic coming to operation for the relief of a complicating hyperthyroidism had best be treated as though his diabetes is complicated by infection, for hyperthyroidism like infection decreases the power of insulin; with the relief of the hyperthyroid state the severity of the diabetes is nearly always much ameliorated.

Postoperative Care.—The total amount of insulin which the patient has been taking preoperatively in twenty-four hours should be given in the twenty-four hours succeeding operation, with this difference only that it is best to divide it into smaller portions and inject every three or four hours; during the twenty-four hours the patient should receive in the form of intravenously administered dextrose the amount of carbohydrate customarily allowed in his diet. Thereafter, dietary readjustment must be made, bearing in mind that the patient not infrequently after operation requires for a while somewhat different insulin dosage than before. The appearance of sugar in the urine at any time shortly after operation, or the signs of hypoglycemia or acidosis, of course require complete accommodation of the treatment to the new conditions.

It will be extremely interesting to see what the effect of the newest type of routine diabetic therapy, that which I have earlier called the "relative disregard of sugar," treatment, is going to be on the postoperative treatment of diabetics. Greene *et al.* (1940) concluded that the incidence of delayed healing and of infection of originally clean wounds bears no relationship to the height of the blood sugar or the amount of glycosuria.

DIABETES IN CHILDREN

The advent of insulin made it possible to treat childhood diabetes with as good success as adult diabetes; the new high carbohydrate-low fat diets have simplified the problem and much eased the parental burden. I think that the reader will find the practical methods of therapy, discussed earlier in this chapter, as applicable to one age as another. The following points merit special mention:

Insulin and Protamine Zinc Insulin.—Practically all childhood cases are relatively severe. Insulin requirements are also higher than for an adult with diabetes of comparable grade, but there is no definite proportional gauge and therefore dosage must be evolved according to the needs of the individual patient. The approach of puberty, especially in girls, often accentuates this difference between childhood and adult utilization of the drug; after sexual maturity has become established, reduction in dosage is usually possible. Protamine zinc insulin is being used by all leaders in diabetic therapy with fully as good results in children as in adults. Joslin (1943) has said that approximately 80 per cent of his children require both protamine and regular crystalline insulin.

"Free" Dieting.—It is interesting that several physicians in Sweden and Germany (see Lichtenstein, 1938, in Bibliography) had begun before the outbreak of War II to use "free" diets in their children; *i.e.*, allowing the child to eat what it wanted and giving enough insulin to prevent ketosis but disregarding slight to moderate hyperglycemia and glycosuria. In short, before the

type of protamine zinc insulin therapy which I have earlier described as "relative disregard of sugar" was instituted, trials of much the same sort were already being made with regular insulin. Here in our own country Bruce is using the "free" diet with great satisfaction in children on protamine zinc insulin. His children are put on a carefully weighed diet at first, but after a month or two are told to measure their food in teaspoons and tablespoons and ounces, being kept of course under close observation and checked at monthly intervals. After a year of carefully measured diet, the patient is then put on a "free" diet. By this is not meant that he is allowed to eat any and everything he wants without exercising any judgment or self-control; he must try to follow the diet he used when it was measured, but without being a slave to it. Bruce makes the point that after a year of training an intelligent child and his parents should know calories and food values and diabetes so well that they can handle the situation with great ease. He has the urine examined twice a day; the specimen on arising should contain no sugar; the one at bedtime should contain a good deal of sugar, but no acetone. It is said that the children on these "free" diets are doing beautifully. They are in splendid health, go to parties and take part in athletics, and do what their playmates do. Indeed, except for their dose of protamine zinc insulin once a day, they lead a normal life. And their parents are unanimous in their feeling that their children are happier and are now like normal children since going on the "free" diet. Bruce says that he has been unable to see that these children have suffered any ill effects whatsoever from this method of treatment.

Exercise.—Proper management comprises full utilization of the insulin-sparing function of exercise, but with the greater lability of childhood metabolic processes the omission of exercise at accustomed times is more dangerous than in adults. Setting-up exercises of definite type and duration have been shown to be well worth instituting during those seasons when spontaneous outdoor exercise is restricted or for routine performance throughout the year by children not temperamentally disposed to be very active. It is well to bear in mind that if the child's treatment is standardized during a preliminary period in hospital, he will require to have his insulin dosage reduced when he returns to normal play activity at home.

Infection.—The effect of infection in reducing insulin efficiency is much more rapid and more marked in children than in adults since children have a relatively smaller reserve of glycogen in the liver. A child completely free of glycosuria, hyperglycemia and acidosis one day may be in coma the next as a result of even the milder sort of acute infectious process. Mirsky and Nelson (1944) stress the importance of frequent feedings of carbohydrate during infections in children.

Acidosis, Coma and Hypoglycemia.—As just stated, the transition from a state of complete control to one of coma may be extremely rapid in children in whom a rigid diet-to-insulin regimen is being followed; a food orgy, or the omission of a dose of insulin, can institute it as rapidly as the onset of infection. Similarly, the omission of a meal, a bout of vomiting, or excessive indulgence in exercise may precipitate hypoglycemic shock quite suddenly in children who are being so carefully controlled. Unfortunately, the prodromal symptoms of either of these opposite states are less typical in children than in adults; therefore any unusual behavior of a diabetic child, such as unwonted irritability, obstinacy, rage, pallor, tearfulness, hunger, drowsiness, or the like, should be quickly analyzed to determine its possible relationship to a sin of omission or

commission. Some physicians, feeling that the symptoms of impending shock form a pattern which is typical for each individual, like deliberately to induce such an experience for educative purposes during the early period of diabetic training; however, that the identical prodromata always appear is denied by many observers.

DIABETES AND PREGNANCY

Effect of Diabetes upon the Mother.—Insulin has unquestionably increased the fertility of diabetic women and it is now the consensus that the fact of pregnancy itself does not offer a very great threat to the life of the diabetic woman provided she is in the hands of a physician who thoroughly understands the treatment of diabetes and is herself fully cooperative; 209 of the 210 consecutive pregnancies of diabetic women reported by Joslin (1945) resulted in survival of the mother. But the sudden changes in tolerance, necessitating dietary and insulin adjustments, are entirely unpredictable, though in the studies of Lavietes *et al.* (1943) of 31 pregnancies in 23 diabetic women, carbohydrate tolerance was observed to fall quite regularly, the most marked fall usually beginning at six to eight months with return to the original level at, or shortly before, term. Women do not always react similarly in each pregnancy: Northmann (1941) reported a patient whose first pregnancy terminated in coma whereas during the course of the second pregnancy there was a remarkable improvement in carbohydrate utilization; Feinblatt *et al.* (1944) have also reported five cases in which the women became dramatically insulin-sensitive during the immediate postpartum period.

Nausea and vomiting during the first trimester demand readjustments so that adequate carbohydrate is kept burning to prevent ketosis. Joslin *et al.* (1940) say this condition can best be handled by hourly feedings and the administration of insulin every three hours, supplementary use of intravenous dextrose to be made if necessary; or if the patient has been on protamine zinc insulin this may be continued and regular insulin used at noon and at 6 P.M. as indicated by tests. It would seem, according to White and Hunt (1943), that in Joslin's group where protamine zinc insulin plus crystalline insulin before breakfast has become practically routine, these extra doses of insulin before lunch and the evening meal are now used in practically all pregnant diabetics in the attempt to prevent the excretion of glucose which is often excessive due to the lowered renal threshold in pregnancy.

Prolonged difficult labor, which occurs more frequently among diabetic than nondiabetic women because of the overweight of the child, centers attention upon the actual period of labor as the most trying from the diabetic standpoint. Not only is there the possibility of a plunge into hypoglycemic shock upon the one hand or ketosis and coma upon the other, but the possibilities of perineal or cervical tears and of postpartum sepsis are undoubtedly greater causes for concern in the diabetic than in the nondiabetic woman. Many observers have felt that cesarean section at about the thirty-sixth to thirty-seventh week is indicated in most instances, but the opinion is not unanimously held. Mengert and Laughlin (1939) reported 33 pregnancies in diabetic women with 28 spontaneous deliveries, 2 breach extractions and only 1 cesarean section, all the operative deliveries being performed because of obstetric indications only; in White and Hunt's (1943) recently reported series of 125 cases, 79 had been delivered by cesarean section and 46 normally.

Diabetic women are seldom able to nurse their infants. Kramer (1935), how-

ever, stressed the point that when lactation begins one should be on guard against a blood-sugar drop, necessitating reduction in insulin dosage.

Effect of Diabetes upon the Infant.—Insulin has not effected a significant reduction in the mortality of the newborn of diabetic women, for still about 30 per cent of all the pregnancies complicated by diabetes mellitus result in

DIABETIC TABLE A.—MAINTENANCE DIETS FOR MEN (BARACH)

Height with Shoes.		Body Frame.	Ideal Weight.		Caloric Requirement at 25 Cal./Kilo.				Caloric Requirement at 27.5 Cal./Kilo.				Caloric Requirement at 30 Cal./Kilo.			
Ft.	In.	Build.	Lbs.	Kilos.	Total per Day	Carb. gm.	Prot. gm.	Fat gm.	Total per Day	Carb. gm.	Prot. gm.	Fat gm.	Total per Day	Carb. gm.	Prot. gm.	Fat gm.
5	2	Small	120	55	1375	130	55	70	1515	150	50	80	1650	170	60	80
5	2	Med.	128	58	1450	150	55	70	1595	160	60	80	1740	180	65	85
5	2	Large	137	62.5	1560	150	60	80	1720	175	65	85	1875	195	70	90
5	3	Small	123	56	1400	140	55	70	1540	150	55	80	1680	175	65	80
5	3	Med.	131	59.5	1485	145	50	80	1635	165	60	80	1785	175	70	90
5	3	Large	138	63	1575	155	60	80	1735	175	65	85	1890	200	70	90
5	4	Small	127	58	1450	150	55	70	1595	160	60	80	1740	180	65	85
5	4	Med.	135	61.5	1540	150	55	80	1690	175	65	80	1845	195	65	90
5	4	Large	143	65	1625	170	55	80	1790	175	70	90	1950	210	75	90
5	5	Small	131	59.5	1485	145	50	80	1635	165	60	80	1785	175	70	90
5	5	Med.	139	63	1575	155	60	80	1735	175	65	85	1890	200	70	90
5	5	Large	147	67	1675	175	65	80	1845	195	65	90	2010	215	85	90
5	6	Small	134	61	1525	155	50	80	1675	175	65	80	1830	195	60	90
5	6	Med.	142	65	1625	170	55	80	1790	175	70	90	1950	210	75	90
5	6	Large	151	69	1725	175	65	85	1900	200	70	90	2070	235	80	90
5	7	Small	138	63	1575	155	60	80	1735	175	65	85	1890	200	70	90
5	7	Med.	146	66.5	1660	175	60	80	1825	190	65	90	1995	215	80	90
5	7	Large	155	70.5	1765	170	70	90	1940	205	75	90	2115	235	80	95
5	8	Small	141	64	1600	165	55	80	1760	170	70	90	1920	205	70	90
5	8	Med.	150	68	1700	180	65	80	1870	195	70	90	2040	210	75	100
5	8	Large	159	72	1800	190	60	90	1980	205	85	90	2160	235	80	100
5	9	Small	146	66.5	1660	175	60	80	1825	185	70	90	1995	205	80	95
5	9	Med.	154	70	1750	180	65	85	1925	205	75	90	2100	230	80	95
5	9	Large	163	74	1850	195	65	90	2035	220	85	90	2220	250	80	100
5	10	Small	150	68	1700	180	65	80	1870	195	70	90	2040	210	75	100
5	10	Med.	158	72	1800	190	60	90	1980	205	85	90	2160	235	80	100
5	10	Large	168	76	1900	200	70	90	2090	230	80	95	2280	265	80	100
5	11	Small	154	70	1750	180	65	85	1925	205	75	90	2100	230	80	95
5	11	Med.	163	74	1850	195	65	90	2035	220	85	90	2220	250	80	100
5	11	Large	173	79	1975	210	80	90	2175	240	80	100	2370	280	85	100
6	0	Small	158	72	1800	190	60	90	1980	205	85	90	2160	235	80	100
6	0	Med.	167	76	1900	200	70	90	2090	230	80	90	2280	265	80	100
6	0	Large	177	80	2010	215	85	90	2215	245	85	100	2400	270	85	110
6	1	Small	163	74	1850	195	65	90	2035	220	85	100	2220	250	80	100
6	1	Med.	172	78	1950	200	75	90	2150	235	80	100	2340	275	85	100
6	1	Large	182	83	2075	230	85	90	2285	260	85	100	2490	285	90	110
6	2	Small	169	77	1925	205	75	90	2115	235	80	95	2310	265	85	100
6	2	Med.	178	81	2025	220	90	90	2230	250	85	100	2430	275	85	110
6	2	Large	188	85.5	2125	235	85	95	2350	280	95	100	2565	280	90	120
6	3	Small	174	79	1975	210	80	90	2175	240	80	100	2370	285	85	100
6	3	Med.	183	83	2075	230	85	90	2285	260	85	100	2490	285	90	110
6	3	Large	193	88	2200	245	80	100	2420	270	85	110	2640	295	95	120

(Above diets are in round numbers: disregard slight inaccuracies.)

the death of the fetus or the newborn infant. In the excellent study of this matter by Miller *et al.* (1944), of the Department of Pediatrics of the Yale Medical School, who studied the 146 births in 143 pregnancies of 123 diabetic mothers, it was found that infant mortality in this group was about five times that in the nondiabetic group. Even under the most favorable conditions the

risk to the infant was about four times that of the normal, and if the mother had severe complications of pregnancy with diabetes, either mild or severe, the risk was about eight times as great. These figures seem to hold whether the mothers were or were not insulin treated. The excessive size of the fetus in diabetic women has been held responsible for part of the high mortality in

DIABETIC TABLE B.—MAINTENANCE DIETS FOR WOMEN (BARACH)

Height with Shoes.		Body Frame.	Ideal Weight.		Caloric Requirement at 25 Cal./Kilo.				Caloric Requirement at 27.5 Cal./Kilo.				Caloric Requirement at 30 Cal./Kilo.			
Ft.	In.	Build.	Lbs.	Kilos.	Total per Day	Carb. gm.	Prot. gm.	Fat gm.	Total per Day	Carb. gm.	Prot. gm.	Fat gm.	Total per Day	Carb. gm.	Prot. gm.	Fat gm.
4	11	Small	108	49	1225	120	50	60	1345	130	50	70	1470	150	50	75
4	11	Med.	114	52	1300	140	50	60	1430	145	55	70	1560	155	55	80
4	11	Large	123	56	1400	140	55	70	1540	150	55	80	1680	175	65	80
5	0	Small	109	49.5	1240	125	50	60	1360	135	50	70	1485	150	50	75
5	0	Med.	116	52.5	1315	145	50	60	1445	150	55	70	1575	155	60	80
5	0	Large	124	56	1400	140	55	70	1540	150	55	80	1680	175	65	80
5	1	Small	111	50.5	1260	130	50	60	1390	140	50	70	1515	145	55	80
5	1	Med.	118	54	1350	130	50	70	1485	150	50	75	1620	170	55	80
5	1	Large	126	57	1425	145	55	70	1570	150	65	80	1710	180	65	80
5	2	Small	114	52	1300	140	50	60	1430	145	55	70	1560	150	60	80
5	2	Med.	121	55	1375	130	55	70	1515	145	55	80	1650	170	60	80
5	2	Large	130	59	1475	150	50	75	1625	170	55	80	1770	170	70	90
5	3	Small	117	53.5	1340	130	50	70	1475	150	50	75	1605	160	60	80
5	3	Med.	124	56	1400	140	55	70	1540	150	55	80	1680	175	65	80
5	3	Large	131	59.5	1485	150	50	75	1635	170	60	80	1785	175	70	90
5	4	Small	120	55	1375	130	55	70	1515	145	55	80	1650	170	60	80
5	4	Med.	128	58	1450	150	55	70	1595	160	60	80	1740	180	65	85
5	4	Large	136	62	1550	150	60	80	1705	180	65	80	1860	195	65	90
5	5	Small	124	56	1400	140	55	70	1540	150	55	80	1680	175	65	80
5	5	Med.	131	59.5	1485	150	50	75	1635	170	60	80	1785	175	70	90
5	5	Large	139	63	1575	155	60	80	1735	180	65	85	1890	200	70	90
5	6	Small	128	58	1450	150	55	70	1595	160	60	80	1740	180	65	85
5	6	Med.	135	61.5	1530	150	55	80	1690	175	65	80	1845	195	65	90
5	6	Large	144	65.5	1640	175	55	80	1800	175	70	90	1965	215	75	90
5	7	Small	131	59.5	1485	150	50	75	1635	170	60	80	1785	175	70	90
5	7	Med.	139	63	1575	155	60	80	1735	180	65	85	1890	200	70	90
5	7	Large	148	67.5	1690	175	65	80	1855	195	65	90	2025	225	80	90
5	8	Small	134	61	1525	150	55	80	1675	175	65	80	1830	195	60	90
5	8	Med.	142	64.5	1610	165	55	80	1775	170	70	90	1935	210	70	90
5	8	Large	152	69	1725	175	65	85	1900	200	70	90	2070	235	80	90
5	9	Small	138	63	1575	155	60	80	1735	180	65	85	1890	200	70	90
5	9	Med.	146	66.5	1660	175	60	80	1825	190	65	90	1995	215	80	90
5	9	Large	156	71	1775	170	70	90	1950	210	75	90	2130	240	80	95
5	10	Small	142	64.5	1610	165	55	80	1775	170	70	90	1935	210	70	90
5	10	Med.	150	68	1700	180	65	80	1870	195	70	90	2040	210	70	100
5	10	Large	159	72.5	1810	190	60	90	1995	215	80	90	2175	235	85	100
5	11	Small	145	66	1650	170	60	80	1815	185	65	90	1980	210	80	90
5	11	Med.	153	69.5	1735	175	65	85	1900	200	70	90	2085	215	80	100
5	11	Large	162	73.5	1835	195	60	90	2020	210	70	100	2205	240	85	100
6	0	Small	147	67	1675	175	65	80	1845	195	65	90	2010	215	85	90
6	0	Med.	157	71.5	1790	175	70	90	1965	215	75	90	2145	225	85	100
6	0	Large	167	76	1900	200	70	90	2090	215	80	100	2280	260	85	100

(Above diets are in round numbers: disregard slight inaccuracies.)

infants by some investigators, but the findings of Miller *et al.* did not substantiate this belief. Furthermore, the long-held belief that the hyperglycemia in the pregnant diabetic woman is responsible for these deaths was not supported since fetal and newborn deaths occurred with about the same incidence before diabetes became manifest in the mother as afterwards. Miller and Wilson

(1943) have found that infants born of diabetic mothers may have cardiac hypertrophy and excessive erythropoiesis in the liver with large numbers of nucleated red blood cells in the peripheral blood during the first days of life, the cardiac and hepatic changes being sometimes associated with hyperplasia of the islands of Langerhans in overweight fetuses. Miller *et al.* found these

DIABETIC TABLE C.—MAINTENANCE DIET FOR GROWING CHILDREN (BARACH)
(50% of Calories from Carbohydrate, 15% from Protein, 35% from Fat)

Age.	Weight.		Maximum diet, normals, daily allowance.				Maximum diet, diabetes, daily allowance.			
Years.	Pounds.	Kilos.	Calories.	Carbohydrate grams.	Protein, grams.	Fat, grams.	Calories.	Carbohydrate, grams.	Protein, grams.	Fat, grams.
½	15	7	700	90	30	25	600	75	25	25
1	20	9	1000	125	40	35	800	100	30	30
2	26	10	1100	140	45	40	880	110	35	35
3	31	14	1200	150	50	45	960	120	40	40
4	35	16	1300	165	50	50	1040	130	40	40
5	38	17	1400	175	55	55	1120	140	45	45
6	43	19	1500	185	55	60	1200	150	45	50
7	50	22	1600	200	65	60	1280	160	50	50
8	55	25	1700	215	65	65	1360	170	55	55
9	61	28	1800	225	70	70	1440	180	55	55
10	67	30	1900	235	70	75	1520	190	55	60
11	75	34	2000	250	70	80	1600	200	65	65
12	81	37	2100	265	80	80	1680	210	65	65
13	90	40	2200	275	85	85	1760	220	70	70
14	103	47	2300	285	85	90	1840	230	70	70
15	112	50	2400	300	90	95	1920	240	75	75
16	126	57	2500	315	95	95	2000	240	80	80
17	133	60	2600	325	100	100	2080	240	80	90
18	138	63	2700	340	100	105	2160	240	85	95
19	138	63	2800	350	100	110	2240	240	90	100
20	139	63	2900	365	100	115	2320	240	95	110

1. After age 16, girls weigh 10% less than boys.
2. Caloric values of diabetic diets are 20% below full normal diets; this may be increased to full normal when desirable.
3. After age 15 when growth rate slows, Carbohydrate portions remain same, Fat may be increased. A lower fat diet may be attained by substituting 2 grams carbohydrate for one gram fat in the daily diet.
4. These diets obtain more calories from Carbohydrate and Protein than from Fats.
5. In these tables fractions have been disregarded in favor of round numbers.

things occurring in infants before symptoms or signs of diabetes could be recognized in their mothers; they felt furthermore that there is no certainty that the lethal factor for the fetus is identical either with the one that produces large fetuses or with the one that leads to the visceral changes in the fetus.

White and Hunt expressed themselves of the opinion, in 1940, that fetal deaths in diabetic women are associated with a high concentration of gonado-

Diabetic Table D.—Carbohydrate Portion of Allowance (Barach)

	Carbohydrate.	50	60	70	80	90	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300
	Food.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.
Breakfast	6 per cent fruit	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	135	200	235	300	365	400	400	400	400	400	400
	Cereal (dry weight)	14	20	25	28	34	23	28	34	37	28	34	40	28	34	37	40	40	40	40	40	40	40	40	40	40	40
	Bread	...	...	...	...	...	20	20	20	20	40	40	40	60	60	60	60	60	60	60	60	60	60	60	60	60	60
Lunch	20 per cent vegetable	50	50	60	70	90	60	70	90	110	120	140	150	170	190	160	170	190	200	170	190	200	225	225	225	225	225
	6 per cent fruit	115	165	185	200	200	200	200	200	200	200	200	200	200	200	200	200	200	235	200	200	235	235	300	300	300	300
	Bread	...	...	...	...	...	20	20	20	20	20	20	20	20	20	40	40	40	40	60	60	60	60	60	60	60	60
Dinner	20 per cent vegetable	50	50	50	50	50	50	70	80	100	120	130	150	170	180	150	170	180	150	170	180	200	225	225	245	245	280
	6 per cent vegetable	60	80	100	100	135	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	300	300	300	300
	6 per cent fruit	60	85	130	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	300	300	350
	Bread	...	...	...	...	...	...	...	...	...	...	...	...	...	...	20	20	20	40	40	40	40	40	40	40	50	50
	Grams protein incidentally obtained, and therefore to be subtracted from Protein-Fat Portion	...	...	5	5	5	5	5	10	10	10	10	10	10	10	15	15	15	15	20	20	20	20	22	22	25	25

tropic substance in the maternal serum during the latter part of pregnancy and that the administration of estrogens and progesterone can prevent the large number of fatalities. In 1943, these workers reported hormone assays made after the twenty-fourth week of pregnancy in 125 consecutive cases of diabetic women. Forty-one of these were classified as normal and 77 as abnormal. Twenty-seven of the latter received no replacement therapy and toxemia developed in 52 per cent of them, premature delivery in 40 per cent and 60 per cent of the fetuses survived. In those to whom substitutional therapy was given it is said that toxemia "appeared to be modified," premature delivery occurred in 25 per cent, and fetal survival was 92 per cent. It would seem that these studies are sufficiently interesting to warrant an attempt at confirmation by some other group.

Diabetic Table E.—Protein and Fat Portion of the Allowance (Barach)

	Protein.	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90
	Fat (incidental).	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90
Break-fast	Grams meat.....	25	30	40	50	55	65	75	80	90	100	105	115	125	130	140	150
Lunch	Grams meat.....	25	35	40	50	60	70	75	85	90	100	110	115	125	135	140	150
Dinner	Grams meat.....	25	35	45	50	60	70	75	85	95	100	110	120	125	135	145	150

Diabetic Table F.—Additional Fat Portion of the Allowance (Barach)

	Additional fat.	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85
Break-fast	Butter.....	4	6	7	10	12	12	15	17	19	21	23	22	22	22	22	22
	Fat, salad or olive oil...																
Lunch	Butter or mayonnaise...	4	6	8	10	12	14	15	17	19	21	23	22	22	22	22	22
	Fat, salad or olive oil...	..	..	..	..	..	..	..	..	..	..	..	3	2	8	12	14
Dinner	Butter or mayonnaise...	4	6	8	10	12	15	17	19	21	23	25	24	24	24	24	24
	Fat, salad or olive oil...	..	..	..	..	..	..	..	..	..	..	3	5	10	10	14	18

Treatment of the Newborn Infant.—Randall and Rynearson (1936), fearing a state of hypoglycemia in the infant due to overfunction of its pancreas, placed the child in an atmosphere of 40 to 50 per cent oxygen in an incubator and injected 5 cc. of 10 per cent dextrose solution into each buttock, repeating 10-cc. doses at such intervals as were dictated by the blood-sugar level, the behavior of the infant, and its ability to take food by mouth. Beginning within four hours if possible, 10 cc. of dextrose solution, or 7 cc. of lactic acid-karo mixture (see below), were given every two hours for the first forty-eight hours if tolerated; thereafter, 30 cc. of the mixture every three hours, but whenever it was poorly taken or behavior indicated hypoglycemia, resort was had again to the intramuscular introduction of dextrose. Mixture: using sterilized utensils, mix 70 Gm. karo syrup and 930 cc. whole milk and boil fifteen minutes; cool until ice cold and add 120 drops of 85 per cent lactic acid solution, drop

Diabetic Table G.—Carbohydrate Exchanges (Slightly modified from Barach's table)

Instructions.—If you wish to have the patient trade some of his fruit or vegetables for milk, cream, bread and butter, or cereal and butter, proceed as follows: find the quantity of the new food and then omit the quantity of fruit or vegetables appearing in the same column. For example: choosing to allow a glass of milk (8 ounces or 240 cc.), find the 240 milk column and then omit the 12 Gm. carbohydrate there stated, either by leaving off 400 Gm. of 3 per cent fruit or vegetable, or 200 Gm. of 6 per cent, or 80 Gm. of 15 per cent, or 60 Gm. of 20 per cent. To even things up completely in this instance, however, 36 Gm. of meat must also be omitted, as shown.

Grams Carbohydrate	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	20	22	24	26	28	30	32	34	36	38	40
3% Vegetable	65	100	135	165	200	235	265	300	335	365	400	435	465	500	535	565	600											
6% Fruit or Vegetable	35	50	65	85	100	115	135	150	165	185	200	215	235	250	265	285	300	335	365	400	435	465	500	535	565	600		
15% Fruit or Vegetable	15	20	25	35	40	50	55	60	65	75	80	85	90	100	105	115	120	135	145	160	175	190	200	210	225	240	255	265
20% Fruit or Vegetable	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	100	110	120	130	140	150	160	170	180	190	200
Take Grams Milk	40	60	80	100	120	140	160	180	200	220	240	260	280	300	320	340	360	400										
Leaving off Grams Carb.	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	20										
and Grams Meat	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	60										
Take Grams Cream	40	60	80	100	120	140	160	180	200	220	240	260	280	300	320	340	360	400										
Leaving off Grams Carb.	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	20										
and Grams Meat	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	60										
and Grams Butter	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	80										
Take Bread + Butter									20 +0	22 +0	24 +0	26 +0	28 +0	30 +5	32 +5	34 +5	36 +5	40 +5	44 +5	48 +6	52 +6	56 +7	60 +7	64 +8	68 +8	72 +9	76 +9	80 +10
Leaving off Grams Carb.									10	11	12	13	14	15	16	17	18	20	22	24	26	28	30	32	34	36	38	40
and Grams Meat									10	11	12	13	14	15	16	17	18	20	22	24	26	28	30	32	34	36	38	40
Take Cereal + Butter									14 +0	16 +0	18 +5	19 +5	20 +5	21 +5	23 +5	25 +5	26 +5	28 +5	32 +6	34 +6	37 +7	40 +8	43 +8	45 +8	48 +9	52 +9	54 +10	57 +10
Leaving off Grams Carb.									10	11	12	13	14	15	16	17	18	20	22	24	26	28	30	32	34	36	38	40
and Grams Meat									10	12	14	14	15	17	18	19	20	21	22	25	28	30	31	32	34	36	38	40

Diabetic Table H.—Percentage Vegetables and Fruits

3 per cent (sometimes called 5 per cent)

Vegetables (fresh)

Artichokes (French, as used for salad)
Asparagus
Beans, green or wax (or canned)
Beet greens
Broccoli
Brussels sprouts
Cabbage
Cauliflower
Celery
Cucumbers
Eggplant
Endive
Green peppers
Leeks
Lettuce
Marrow
Mustard greens
Okra
Pickles (sour)
Radishes
Rhubarb
Sorrel
Sauerkraut (or canned)
Spinach
Summer squash
Swiss chard
Tomatoes
Watercress

6 per cent (sometimes called 10 per cent)

Vegetables

Beets
Carrots
Dandelion greens
Kale
Kohlrabi
Onions
Oyster plant
Pumpkin
Rutabaga
String beans
Squash
Turnips

Fruits

Avocado
Blackberries
Cranberries
Gooseberries
Grapefruit
Lemons
Limes
Muskmelons, cantaloupe, honey dew
Oranges
Peaches
Pineapple
Strawberries
Tangerines
Watermelon

15 per cent

Vegetables

Artichokes (Jerusalem, or "ground," fresh; when cut into chips and dried, reckon the C value per Gm. doubled.)
Green peas
Lima beans (canned)
Parsnips
Salsify
Yams

Fruits

Apples
Apricots
Blueberries
Cherries
Currants
Grapes
Guavas
Huckleberries
Nectarines
Papaws
Pears
Plums
Quinces
Raspberries

20 per cent or higher

Vegetables

Baked beans
Shelled beans
Green corn
Potatoes (baked or boiled)
White
Sweet

Fruits

Bananas
Figs (fresh)
Prunes

Diabetic Table I.—Meat Exchanges (Barach)

Instructions.—If your patient wishes to trade about among the meats, or to substitute fish, cheese, or eggs for some of his meat allowance, this can be easily arranged for him. For example, suppose his protein allowance has been stated in Table G as 100 Gm. meat for dinner. Let us say he has been taking this in the form of 70 Gm. chicken or turkey plus 8 Gm. butter, as shown in the Table (below) in the 100 Gm. meat column, but that, like a chap I know, he would prefer a tasty bit of American cheese; you need then only have him omit his 70 Gm. of chicken or turkey, and the 8 Gm. butter which go with it, and take on 69 Gm. American cheese, dropping at the same time another 6 Gm. of butter.

(Cooked Meats) GRAMS OF MEAT	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130	135	140	145	150
LEG OF LAMB plus Butter	25 +2	30 +3	35 +3	40 +4	45 +4	50 +4	55 +4	60 +4	65 +5	70 +5	75 +6	80 +6	85 +7	90 +7	95 +7	100 +8	105 +8	110 +8	115 +9	120 +9	125 +10	130 +10	135 +11	140 +11	145 +12	150 +12
ROUND STEAK plus Butter	18 +4	21 +4	25 +5	28 +6	32 +7	36 +8	39 +8	43 +9	47 +10	50 +11	54 +12	56 +13	61 +14	64 +15	68 +16	72 +16	75 +16	78 +17	82 +18	86 +19	90 +20	93 +20	97 +21	100 +22	104 +23	108 +24
SIRLOIN STEAK plus Butter	20 +4	25 +4	29 +5	33 +5	37 +6	42 +7	46 +7	50 +8	54 +9	58 +9	62 +10	66 +11	70 +12	74 +13	78 +14	83 +14	88 +15	92 +16	96 +17	100 +18	104 +18	108 +19	112 +20	116 +20	120 +21	124 +21
CHICKEN OR TURKEY plus Butter	16 +2	20 +2	24 +2	28 +3	31 +3	35 +4	38 +4	42 +4	45 +4	48 +5	52 +5	56 +6	60 +6	64 +7	67 +7	70 +8	73 +8	76 +9	79 +9	82 +10	86 +10	90 +11	94 +11	97 +12	101 +12	105 +12
DRIED BEEF plus Butter	16 +4	20 +5	24 +6	27 +7	30 +8	34 +9	37 +10	40 +11	43 +12	46 +13	50 +14	53 +15	56 +16	59 +17	62 +18	66 +18	69 +19	73 +20	76 +21	80 +22	83 +23	86 +24	89 +25	92 +26	96 +27	100 −28
CORNED BEEF plus Butter	18 +1	22 +1	26 +2	30 +2	34 +2	38 +3	42 +3	46 +3	50 +3	54 +4	57 +4	60 +4	64 +5	68 +5	72 +6	76 +6	80 +7	84 +7	86 +7	92 +8	96 +8	100 +8	104 +8	108 +9	112 +9	115 +9
LAMB CHOPS, ROAST BEEF minus Butter	22 −2	26 −2	30 −2	35 −3	40 −3	45 −4	50 −4	55 −4	60 −5	64 −5	68 −5	72 −6	76 −6	80 −7	85 −7	90 −7	95 −8	100 −8	104 −8	109 −8	114 −8	118 −9	122 −9	127 −10	131 −10	136 −11
LIVER (weigh raw) plus Butter	25 +5	30 +6	35 +7	40 +8	45 +9	50 +10	55 +11	60 +12	65 +13	70 +14	75 +15	80 +16	85 +17	90 +18	95 +19	100 +20	105 +21	110 +22	115 +23	120 +24	125 +25	130 +26	135 +27	140 +28	145 +29	150 +30
TONGUE (pickled) minus Butter	38 −3	46 −3	54 −4	62 −5	70 −6	77 −7	85 −7	92 −8	100 −9	108 −10	115 −10	123 −11	131 −11	139 −12	146 −13	154 −14	162 −14	168 −14	177 −15	184 −16	192 −17	200 −18	208 −19	215 −20	223 −21	230 −21
FRIED HAM minus Butter	22 −2	26 −2	30 −3	35 −3	40 −4	45 −5	50 −5	55 −5	60 −6	64 −6	68 −7	72 −7	76 −8	80 −9	85 −10	90 −10	95 −11	100 −11	104 −12	109 −12	114 −12	118 −13	122 −13	127 −14	131 −14	136 −15

FRESH HAM STEAK minus Butter	15 −2	18 −2	21 −3	24 −3	27 −4	30 −4	33 −5	63 −5	39 −5	42 −6	45 −6	48 −7	51 −7	54 −7	57 −8	60 −8	63 −8	66 −9	69 −9	72 −10	75 −10	78 −11	81 −11	84 −11	87 −12	90 −12
SPARE RIBS minus Butter	20 −3	24 −3	28 −4	32 −4	36 −5	40 −6	44 −6	48 −7	52 −8	56 −9	60 −10	64 −10	68 −11	72 −11	76 −12	80 −12	84 −13	88 −13	92 −14	96 −14	100 −15	104 −15	108 −16	112 −16	116 −17	120 −18
FRIED HAM minus Butter				9 −1	14 −2	18 −4	23 −4	28 −4	32 −4	36 −5	40 −5	45 −6	50 −7	27 −4	32 −5	36 −5	40 −5	45 −6	50 −8	55 −8	60 −9	64 −9	68 −10	72 −10	76 −11	82 −11
and Eggs				1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2
*BACON (Lean) weigh raw minus Butter	34 −10	40 −12	47 −14	54 −16	60 −18	67 −20	73 −22	80 −24	87 −26	94 −28	102 −30	107 −32	113 −34	120 −36	127 −38	134 −40	140 −42	146 −44	153 −46	160 −48	167 −50	174 −52	180 −54	188 −56	195 −58	201 −60
TUNA FISH, SARDINES (canned) plus Butter	21 +1	26 +1	30 +1	34 +1	39 +1	43 +2	47 +2	51 +2	55 +2	59 +2	63 +3	68 +3	72 +3	76 +3	80 +3	84 +4	89 +4	93 +4	98 +4	102 +4	106 +5	110 +5	114 +5	118 +5	122 +5	126 +6
SALMON (canned) plus Butter	22 +2	26 +2	30 +3	35 +3	40 +4	45 +5	50 +5	55 +5	60 +6	64 +6	68 +7	72 +7	76 +7	80 +8	85 +9	90 +10	95 +10	100 +11	104 +10	109 +11	114 +12	118 +13	122 +13	127 +14	131 +14	136 +15
SPANISH MACKEREL plus Butter	20 +4	25 +4	29 +5	33 +6	37 +7	42 +8	46 +9	50 +10	54 +11	58 +12	62 +12	66 +13	70 +13	74 +14	78 +15	83 +16	88 +16	92 +17	96 +18	100 +19	104 +20	108 +20	112 +21	116 +22	120 +23	124 +24
BLUE FISH plus Butter	18 +5	22 +5	26 +6	30 +7	34 +8	38 +9	42 +9	46 +10	50 +11	54 +12	57 +13	60 +14	64 +15	68 +16	72 +17	76 +18	80 +19	84 +20	86 +21	92 +22	96 +22	100 +23	104 +24	108 +25	112 +26	115 +27
SALT COD plus Butter	20 +7	24 +8	28 +9	32 +10	36 +11	40 +12	44 +14	48 +15	52 +16	56 +17	60 +18	64 +20	68 +21	72 +22	76 +23	80 +24	84 +26	88 +27	92 +28	96 +29	100 +30	104 +32	108 +33	112 +34	116 +35	120 +36
SHAD, WHITE FISH, HALIBUT, LAKE TROUT plus Butter	Approx. Values		24 +2	28 +3	31 +3	35 +4	38 +4	42 +4	45 +4	48 +5	52 +5	56 +6	60 +6	64 +7	67 +7	70 +8	73 +8	76 +9	79 +9	82 +10	86 +10	90 +11	94 +11	97 +12	101 +12	105 +12
AMERICAN CHEESE minus Butter	16 −1	19 −1	24 −2	27 −2	30 −3	34 −3	37 −3	40 −4	44 −4	48 −4	52 −4	55 −5	58 −5	62 −5	66 −6	69 −6	73 −7	76 −7	79 −7	83 −7	86 −7	90 −8	93 −8	97 −8	100 −9	104 −9
COTTAGE CHEESE plus Butter	24 +6	30 +8	36 +9	40 +10	44 +11	48 +12	52 +14	57 +15	62 +16	66 +17	71 +18	76 +20	81 +21	86 +22	91 +23	96 +24	100 +26	105 +27	109 +28	114 +29	119 +30	124 +32	128 +33	132 +34	137 +35	142 +36
EGGS	1	1	1	1	2	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4	4	5	5	5

* Bacon to be broiled until crisp—placed on paper to absorb fat.

by drop while stirring; do not warm too much for feeding, or the mixture may curdle.

I think it should be noted that the more recent studies of Hartmann and Jandon (1937), Miller and Ross (1940), and Sisson (1940) cast some doubt upon the significance of the hypoglycemia in these infants since the blood-sugar level is apparently often low in infants born to nondiabetic mothers.

Diabetic Table J.—Supplementary Information on Food

Diabetic Foods.—Most of the commercial "diabetic foods" are very low in carbohydrate but many of them are also high in protein. It is best to forbid their use.

Saccharin.—Benzosulfimide (saccharin) is an antiseptic and tends to hinder slightly the action of the digestive ferments; an excessive quantity of it may, therefore, impair digestion. More than 5 grains (0.32 Gm.) per day has been pronounced harmful by the Government Referee Board of Chemists, but Bastedo (1942) doubtless expressed the consensus in pronouncing it nontoxic in any amounts that could ordinarily be consumed. Certainly in the moderate doses in which it is used for sweetening beverages of diabetics, it is not likely to do harm. Cooking makes it somewhat bitter; add it late. As a flavored vehicle in which medicines may be administered to the diabetic, the following serves, being similar in taste to aromatic elixir (of course if ingredients are to be added which are not highly soluble in water, such as terpin hydrate for example, the alcoholic content will have to be much increased):

Compound spirit of orange	♏x	0.60
Gluside (saccharin)	gr. j	0.06
Alcohol	℥j	30.00
Water to make	℥iv	120.00

Glycerin.—This substance may also be used in sweetening the food of diabetics in alternation with saccharin.

Seasoning.—Any of the ordinary seasoning agents may be used without reckoning them as food, except that tomato catsup must be employed sparingly.

Jerusalem Artichoke.—The bubble of this tuber's superiority was pricked by the studies of Soskin *et al.* (1931), Stein *et al.* (1931), and Campbell (1934); reckon it as any other 15 per cent vegetable.

Beverages.—Alcohol supplies energy to the body without yielding dextrose or fatty acids, but diabetics away from home and alone should not drink any alcoholic beverages lest an insulin reaction be mistaken for intoxication if there is "liquor on the breath." *Whiskey, gin, rum:* 1 ounce (32 cc.) will yield about 112 calories and need not be reckoned as food in the diabetic sense; but if it is desired to replace food with it, then this amount will permit the omission of 28 Gm. carbohydrate or 12 Gm. fat. *Brandy* often has sugar added to it and should not be used. *Cordials*, such as anisette, benedictine, chartreuse, creme de menthe, curaçao, kümmel, etc., are very high in sugar and are to be forbidden. *Beer and ale* may be reckoned as containing not quite so much alcohol in a glass of 8 ounces (240 cc.) as there is in 1 ounce of whiskey; they will therefore supply nearly as many calories which do not require insulin for their production. But a glass of either of them will contain about 12 Gm. of carbohydrate that must be taken into account. *Wines and cider* vary too much in their sugar content to be safe. *Ginger ale:* reckon about 20 Gm. of carbohydrate to the 8-ounce (240 cc.) glass. *Grape juice* is quite variable but the greatest amount of carbohydrate that a small glass (4 ounces, 120 cc.) is likely to contain is 24 Gm. *Cocoa:* 1 large cup (8 ounces milk, 2 level teaspoonfuls cocoa, 1 level teaspoonful sugar), about 34 Gm. carbohydrate, 8 Gm. protein and 10 Gm. fat. *Tea and coffee:* without sugar and cream, no food value; with sugar and cream (1 large cup, 2 teaspoonfuls cream, 1 level teaspoonful sugar), equivalent to 10 Gm. carbohydrate and 2 Gm. fat.

Oysters.—One-half dozen on shell, 4 Gm. carbohydrate, 6 Gm. protein, 1 Gm. fat.

Canned Shrimp.—One hundred Gm. contain 25 Gm. protein, 1 Gm. fat.

Olives.—Five ripe olives (or 10 green ones), 1 Gm. carbohydrate, 5 Gm. fat.

Soup.—Bouillon or consommé, skimmed of fat and strained, has no food value; this is true of most canned bouillons and bouillon cubes. Creamed soups are rich and variable and should not be used.

Macaroni (Cooked).—Reckon 1 cupful (200 Gm.) at 30 Gm. carbohydrate, 6 Gm. protein 3 Gm. fat.

Crackers.—Twenty Gm. of crackers (3 grahams, or 3 sodas, or 5 small saltines) may be reckoned at about 15 Gm. carbohydrate, 2 Gm. protein, 2 Gm. fat.

Mushrooms.—Two hundred Gm. contain about 1 Gm. fat; the protein and carbohydrate are largely unassimilable and need not be reckoned with.

Nuts.—The assimilable carbohydrate in 50 Gm. of almonds may be reckoned at only 2 Gm., but protein runs 10 Gm. and fat 26 Gm.; Brazil nuts, 3 Gm. carbohydrate, 8 Gm. protein, 35 Gm. fat; chestnuts, 20 Gm. carbohydrate, 3 Gm. protein and 3 Gm. fat; peanuts, 3 Gm. assimilable carbohydrate, 13 Gm. protein, 20 Gm. fat; pecans, 7 Gm. carbohydrate, 5 Gm. protein, 35 Gm. fat; English walnuts, 7 Gm. carbohydrate, 8 Gm. protein, 32 Gm. fat; black walnuts, 5 Gm. carbohydrate, 14 Gm. protein, 28 Gm. fat.

Gelatin.—Contains 85 per cent protein, practically no other food constituent; in sweetening, bear in mind that each level teaspoonful of sugar yields 20 Gm. carbohydrate.

Ice Cream.—A portion (100 Gm.) of average commercial ice cream may be reckoned at 20 Gm. carbohydrate, 4 Gm. protein and 14 Gm. fat.

Milk.—A glass (240 cc.), 12 Gm. carbohydrate, 8 Gm. protein, 10 Gm. fat.

Butter and Oleomargarine.—Ten Gm. (a restaurant "square"), 8.5 Gm. fat; therefore the purist will frown just a little at an equal exchange of 1 Gm. butter or margarine for 1 Gm. oil or fat (see below).

Oils and Fats.—Lard, fat, Crisco, olive and salad oils are fat, Gm. for Gm. (see Butter above).

Eggs.—Reckon 1 egg of average size at 6 Gm. protein and 6 Gm. fat.

Sugar.—Sugar is carbohydrate, Gm. for Gm.

Bread.—The difference between white, rye, and whole wheat are too slight to be of importance, 1 ordinary slice (½ inch, 30 Gm.), 16 Gm. carbohydrate, 3 Gm. protein.

HYPERINSULINISM AND IDIOPATHIC FUNCTIONAL HYPOGLYCEMIA

The well-known reaction to the injection of an overdose of insulin in the treatment of diabetes is due to the induction by this exogenous method of a temporary state of hypoglycemia; in recent years we have come to recognize a similar condition due to endogenous factors. That is to say, there are individuals, nondiabetic, who develop a state of hypoglycemia with all the attendant symptoms of insulin shock as described in Diabetes. Seale Harris, of Birmingham, Alabama, who first presented the entity in 1924, called it "hyperinsulinism," describing at the same time a state of "dysinsulinism" in which the condition of hypoglycemia was at times succeeded by a temporary one of hyperglycemia; a relatively large number of cases has since been reported. The epileptoid character of the convulsions in some of the severe cases has also given rise to the opinion that perhaps a number of individuals convicted of idiopathic epilepsy may be in reality sufferers from this newly recognized metabolic dyscrasia, but the studies of Ziskind *et al.* (1936) certainly caused doubt that the relationship is a very frequent one. Cameron (1930) pointed out the ease with which night terrors in children are sometimes relieved by the administration of sugar; bizarre fatigue states in youngsters might also be hypoglycemic reflections, since comparable states of aggravating restlessness, obstinacy and silliness have been noted at times in adults preceding the onset of unconsciousness; indeed, Harris (1936) and others have shown that hyperinsulinism may simulate or be the underlying cause of many of the syndromes classified as neuroses or psychoses; Weinstein and Mattikow (1939), furthermore, reported 2 cases in which angina pectoris was the predominating symptom. Attacks frequently appear when the blood sugar level has reached 70 mg. per 100 cc., but not invariably; sometimes a patient will be in a serious state

at 50 mg., while at another time he will have only mild symptoms or none at all at the same level. In fact, Hart and Lisa (1940), in confirmation of other observers, found that in individuals not affected with this malady routine fasting blood-sugar levels frequently fall below 80 mg.; that values under 70 without shock symptoms are common; and that there may be times when the blood sugar reaches as low as 28 mg. without a reaction. Obviously then, it is only a low blood sugar accompanied by symptoms that will make the presumptive diagnosis possible.

It now seems that the study of this disease is facilitated by considering each case as either one of organic hyperinsulinism, hypoglycemia secondary to hepatic disease, or functional hypoglycemia —at least Conn, who studied the matter for a number of years, expressed the opinion, in 1940, that 80 to 90 per cent of the cases will fall into these three categories. It therefore seems advisable to orient the therapeutic consideration toward this classification.

THERAPY

Organic Hyperinsulinism.—Barring the very rare instances in which the syndrome is associated with hypofunction of the anterior pituitary gland or the adrenal cortices, the term "organic" applies here to an abnormality of the pancreas, *i.e.*, an adenoma, a carcinoma, or generalized hypertrophy and hyperplasia of the islands of Langerhans. Of course the remedy is surgical. Conn's indications for exploration of the pancreas are: (*a*) absence of extrapancreatic causes of hypoglycemia; (*b*) abnormally low level of blood sugar during symptoms and rapid relief by administration of dextrose; (*c*) repeated fasting blood-sugar levels below 50 mg. per 100 cc. when the patient has been eating an adequate diet; (*d*) depression of the fasting blood-sugar level below 40 mg. per 100 cc. by carbohydrate restriction. The value of the glucose tolerance test as an aid to diagnosis is a quite controversial question. More recent evidence favors the insulin tolerance test (Fraser *et al.* 1938; Burtness *et al.*, 1941) in which 5 units of regular insulin are given intravenously after twelve hours of fasting; it is said that two hours later there is no tendency for the blood-sugar level to reach normal if an adenoma of the islets is present. John (1935) has used another sort of insulin test as a differential aid (see below under Functional Hypoglycemia). Complete cure has often resulted from the removal of an adenoma but several operations are often necessary to find the new growth or to locate and remove all the new growths—witness the case of Ziskind *et al.* (1937) in which autopsy revealed an adenoma which had not been found at two previous pancreatic resections, and that of Rayner and Rogerson (1943) in which at a second operation an adenoma was found in the head of the pancreas only after the duodenum and the head had been mobilized. Holman *et al.* (1943) reported the following bizarre occurrences: (*a*) a case in which the removal of one intrapancreatic adenoma failed to give relief but in which removal of a second islet adenoma in the gastrosplenic ligament produced complete cure; (*b*) a case of heterotopic islet adenoma of the duodenum without hypoglycemic symptoms; (*c*) a case of islet carcinoma apparently engrafted on a calcified islet adenoma which presumably had been responsible for hypoglycemia of varying severity during sixteen years; (*d*) a case of hypoglycemia in which exploration of the abdomen revealed no adenoma but isolation of the pancreas from all surrounding structures without interruption of its arterial supply resulted in apparent cure. Sometimes simply partial or subtotal pancreatectomy is resorted to but the results are often disappointing; Conn points

to the likelihood that in the successful cases very small, perhaps only microscopic, tumors have been removed.

Patients who refuse operation can only be treated as cases of functional hypoglycemia, without much prospect of success.

Hypoglycemia in Hepatic Disease.—To rule out the possibility of an impairment of the glycogenic function of the liver acting in the causative role, it seems advisable to employ all the available tests of liver function. At least as recently as 1940 it was the contention of Coller and Jackson and of Conn (1940), of the same group at the University of Michigan, that the glycogenic liver function may be disturbed by gallbladder disease and, therefore, that in certain instances of hypoglycemia cholecystectomy may be called for. Conn's indications are: (*a*) postabsorptive hypoglycemia markedly intensified by dietary carbohydrate restriction; (*b*) postprandial hyperglycemia with intermittent glycosuria; (*c*) hyperglycemic plateau type of dextrose tolerance curve with abnormally low fasting level; (*d*) evidence of impaired function by other tests; (*e*) evidence of a diseased gallbladder by cholecystography; (*f*) presumptive elimination of other causes of chronic degenerative and destructive lesions of the liver.

Patients in this category who refuse operation can only be treated as cases of functional hypoglycemia. Rector and Jennings (1937), reporting 11 cases of hypoglycemia with recurrent convulsions in infants and young children and reviewing previous reports, felt that in this group hypoglycemia is usually a functional hepatic disorder of intermittent character resulting from temporary depletion of glycogen reserve.

Functional Hypoglycemia.—A few of these cases, in which there are no evidences of hepatic, pancreatic, or other organic involvement, are seen in pregnancy and lactation, in individuals who are at severe continuous muscular work, or in cases of very severe renal glycosuria, but in most instances the good old term "idiopathic" must still be applied. These are, however, the cases which usually respond to dietary treatment; occasionally drugs are also helpful.

Dietetics.—In cases of mild severity the taking of a little food that is high in quickly assimilable carbohydrate, between meals and late at night, is usually sufficient to control the symptoms; the frequent drinking of sweetened orange juice or lemonade and the munching of candy is successfully resorted to by many individuals who have recognized the necessity of frequent feeding in their own cases. In going over collected case reports one not infrequently encounters the statement that the patient has for a long time been setting his clock to awaken him in the early morning hours for the snack of food which will prevent his lying helpless in bed at the time when he should arise for the day. These facts being recognized, not unnaturally in the beginning of the study of this disease patients were put on high carbohydrate diets, but soon it was realized that these diets very frequently resulted in an increased number of attacks, the large amounts of carbohydrate ingested affording an added stimulus to insulogenesis with a resultant quick slide into hypoglycemia.

The first definite advance in the dietetic treatment consisted in the use of a diet low in carbohydrate, high in fats, normal or slightly below normal in proteins, and frequent feedings. Harris, the originator of this regimen, believes that there is advantage in using the low percentage fruits and vegetables since their slow digestion yields only small quantities of glucose at a time, by which he believes that the minimum stimulation of insulin secretion is accomplished. Fats, particularly in the form of cream and milk, given with and between

meals, are believed to delay assimilation of carbohydrate by inducing slow emptying of the stomach. The diet in each case must of course meet the patient's nutritional requirements. For adults of average height and weight, Harris allows about 2250 calories, 90 to 150 Gm. of carbohydrate, 60 to 75 Gm. of protein and the rest fats, largely cream and butter, this being divided among five to seven daily feedings. (The reader will find dietetic tables under Diabetes.) Obesity is a not infrequent accompaniment of hyperinsulinism. In such cases, Harris uses 120 Gm. of carbohydrate, 60 Gm. of protein and only 60 Gm. of fats (1260 calories), with six to eight feedings daily. Activities are restricted and the carbohydrate increased to 150 to 200 Gm., or even more if the patient becomes weak or is losing more than 2 pounds (900 Gm.) weight per week. Underweight, asthenic patients are allowed 90 to 150 Gm. carbohydrate, 200 to 300 Gm. fats and 60 to 75 Gm. protein, with five or six feedings a day.

The next advance consisted in the substitution of a high protein for a high fat diet by Conn, who justified his diet upon the following basis: (*a*) Protein is absorbed slowly. (*b*) Protein yields about 58 per cent of itself as carbohydrate but it does so very slowly and there results no hyperglycemia and consequently no resultant hypoglycemia. Conn's recommended diet contains 120 to 140 Gm. of protein, 50 to 75 Gm. of carbohydrates and the remainder fats in order to make up the necessary calories for maintenance; he said that Wilder had also had good results at the Mayo Clinic, using about 2 Gm. of protein per kilogram (2.2 Gm.) body weight. Thorn *et al.* (1943), experimenting in a normal subject, found when using diets of equal caloric value that the high protein meal caused a sustained increase in metabolic rate, that a transient increase in rate followed by a fall below the basal rate followed the high carbohydrate meal, and that no significant increase in rate followed the ingestion of a high fat meal.

Drugs.—Epinephrine (*adrenalin*), in the usual dose of 0.5 to 1 cc. of the 1:1000 solution, is used to rouse the patient from a severe attack. Conn (1940) found that supplementing the high protein dietary regime with subcutaneous injections of small amounts of the drug twice daily sometimes satisfactorily kept the blood sugar above the attack level and did so without increasing the oxidation of carbohydrate. He thought it likely that "slow epinephrine" (see Asthma) might be a valuable adjunct to therapy in some cases. *Ephedrine* has been used only with doubtful results so far. *Pituitrin*, in injections of 0.5 to 1 cc., is sometimes effective in emergencies, as is also *caffeine* in the form of caffeine sodiobenzoate, 5 grains (0.3 Gm.) or more. Harris says that a cup of coffee or a glass of Coca Cola is so effective as to serve in some instances as a diagnostic test. Allan proposed the use of *thyroid substance* as in myxedema, but after several years' trial he stated, in 1935, that he felt it did not give substantial results. John (1935) felt that in functional cases if *insulin* is given hypodermically after meals before the postprandial blood-sugar rise stimulates the production of insulin, the amount of endogenous insulin will remain low enough to prevent hypoglycemic symptoms. He gave 10 to 20 units of insulin after meals and was highly pleased with the results. Harris finds *phenobarbital* helpful in doses of $1\frac{1}{2}$ grains (0.1 Gm.) night and morning in cases difficult to control or in patients who will not adhere to the diet; *bromides* are also effective, it seems, but he counsels against their employment because of bromism. Occasionally he has obtained good results with *belladonna;* however, Quigley (1937) has warned against the use of atropine.

To bring a patient out of an attack when he cannot cooperate to the extent of swallowing sugar or orange juice, the intravenous injection of *dextrose* must be resorted to: 10 Gm. in 50 to 100 cc. of sterile physiologic salt solution, or, as preferred by some men, a smaller amount of a more concentrated solution.

DIABETES INSIPIDUS

Diabetes insipidus is a disease characterized by the excretion of quite enormous amounts of urine and a resultant loss of tissue fluids which has to be compensated by the ingestion of equal quantities of water. The urine is practically colorless, does not contain sugar, is of very low specific gravity, and contains none of the elements suggestive of renal involvement. There is a decrease in the flow of saliva, the mucus becomes thick and tenacious, there is constipation, practically no sweating, and the skin becomes very harsh and dry. The patients are made very miserable by the necessity to urinate so often and to be constantly drinking water. This excessive water drinking usually causes the appetite to become abnormal because of the necessity for a great number of calories in order to bring all the water to body temperature; if, as is often the case, only cold water will be taken, there is in addition shivering, "gooseflesh," weakness and tremor. The disease may occur at any age but is more frequent in young adults; in recent years a great many cases have been described. The onset is usually gradual though in some instances it has been quite sudden. Brown and Rynearson (1944) say that at the Mayo Clinic in order to facilitate diagnosis they have the patient refrain from drinking any fluids for as long a period as he can without extreme discomfort, and then a specimen of urine is obtained. In 29 of their 34 cases the specific gravity of this specimen was less than 1.010, and in four of the five cases it was 1.011.

Cranial injuries, brain tumors, encephalitis and other diseases of the central nervous system (especially syphilis), abdominal aneurysm, tuberculous peritonitis, and other disturbances have been associated with diabetes insipidus a number of times, but in many cases it is not possible to trace a connection of this sort. It would seem that in this disease the pituitary body is at fault through failure to supply a necessary hormone from its posterior portion, but at present we have little more precise information than this fact. There is now conclusive evidence that the disease also exists in an hereditary form which is compatible with the normal length of life in those surviving infancy. Blotner's (1942) review of the literature shows that it may be transmitted for many generations in a family through the maternal or paternal side to either male or female children.

Diabetes insipidus was described by Johann Peter Frank, in 1794. Cushing and his coworkers first drew attention to the apparent hypophyseal relationship in 1912.

THERAPY

Pituitrin.—In the vast majority of cases hypodermic injections of pituitrin control the symptoms of this disease; that is to say, the polyuria ceases or is very markedly reduced and there is then a corresponding decrease in the craving for water. The dose necessary to accomplish relief is usually 1 cc. of obstetrical pituitrin, or of pitressin, but the duration of the relief varies from

four to forty-eight hours; in 16 of a series of 26 cases reported by Rowntree, it was twenty-four hours at least. Most patients prefer to take the injection at night in order to have their greatest period of freedom during the sleeping hours, for the necessity to be urinating frequently throughout the night is one of the most distressing features of the disease. Since peristalsis is sometimes markedly increased by pituitrin, it is advisable to have the injection taken about two hours before bedtime in order to permit a visit to the stool before retiring. The continued use of the drug over a long period of time gives rise to no serious untoward effects; however, it may be wise to counsel cessation of water ingestion very soon after taking the injection, for with a sudden decrease in water elimination there is some danger of water "intoxication" if fluid continues to be poured into the system.

Blumgart reported a series of cases in which intranasal application of the pituitrin was fully as satisfactory as subcutaneous injection. From 0.5 to 5 cc. of obstetrical pituitrin was sprayed into the nose every three to four hours, or a cotton plug soaked in 1 cc. was introduced high up into the nasopharynx of one nostril at a time at intervals of four or more hours. Rowntree also stated that he has had good results with this method. Vidgoff (1932) obtained satisfactory results with freshly desiccated powdered posterior pituitary tissue applied to the nasal mucosa by means of the fingertip. Extract incorporated in jelly was found to be less effective and more expensive. Smith (1934) had 40 to 50 mg. of the powder blown up into the nose from a powder blower; Marble (1935) used this method also, it being much cheaper than any of the others, but one of his patients successfully took the powder in the old-fashioned method of taking snuff, as did Canelo and Lisser's (1935) patient also. Greene and January (1940), Blotner (1942), Court and Taylor (1943) and Jones (1944) reported the satisfactory intramuscular injection of a suspension of pitressin tannate in oil; the duration of action of an injection in Blotner's seven cases of idiopathic origin was forty-eight to sixty hours and in the one case in which the syndrome resulted from brain tumor the duration was thirty hours; the usual dose of this preparation is 1 cc.

In 1932, Zondek and his associates in Germany described a new substance—intermedin—derived from the pars intermedia of the pituitary body. Sulzberger (1933) used the preparation obtained from Zondek successfully in 2 cases, in the United States, and Turner (1935), using a preparation made for him by Parke-Davis, was successful in his 5 cases, though response was not so great as with pituitrin. Dischreit (1935), in Germany, apparently failed completely.

Miscellaneous Measures.—Scherf (1932) reported 5 cases treated with large doses (30 grains, 2 Gm., daily for five days) of amidopyrine (pyramidon), in 4 of which marked diminution in symptoms was induced. The effect was of only short duration but could be obtained again after a short interruption of the treatment; the effectiveness of pituitrin was not altered by changing for a while to amidopyrine. De Gowin (1935) confirmed the efficacy of this drug; however, because of its tendency to cause agranulocytosis, it should be used only under hematologic control.

Treatment of associated diseases, such as syphilis, is of course indicated and will nearly always result in an improvement in the general health; such measures alone rarely bring about any reduction in the polyuria, however. Surgical removal of associated tumors has sometimes corrected the condition. Rowntree said "Spinal puncture is a desirable procedure in all cases, unless contraindicated by the presence of an intracranial neoplasm," though it is not

apparent in the record that it was worth much in his series of cases; cures have followed upon this procedure, but it is well to bear in mind that spontaneous cure is not unknown in this unique disease.

It is usually the practice to reduce the patient's intake of sodium chloride to the practically irreducible minimum, a measure which in itself is often very helpful. In confirmation of earlier experimental findings, Peters (1944) reported a case in which the polyuria was suppressed by starvation occasioned by the vomiting of pregnancy.

Blotner and Cutler (1941) performed total thyroidectomy in 3 cases; in 2 cases, which were of postencephalitic origin, the results were satisfactory but in 1 case, which was idiopathic in nature, there was no effect, though the authors felt this failure was likely due to the presence elsewhere of accessory thyroid tissue. In Findlay's (1937) case, ablation of the thyroid was no more effective in reducing urine output than a low salt diet but it did increase the patient's responsiveness to pitressin and diminish his diuretic response to sodium chloride.

Weinstein and Spingarn (1940) reported a case following, and presumably incited by, a middle ear infection, which terminated after deep roentgen therapy to the pituitary region.

DISTURBANCES IN MENSTRUATION

AMENORRHEA, HYPOMENORRHEA, OLIGOMENORRHEA AND DELAYED MENSTRUATION

The first of these terms means absence of menstruation, the second scanty menstruation, the third infrequent menstruation, and the fourth what the term implies. Other than menopause, of which it is one of the signs, the most frequent cause of amenorrhea is of course pregnancy and the height of lactation. Other very simple things may bring about these disturbances, especially in girls and younger women, such as change in climate or environment, a love affair, exciting or frightening emotional experiences, and the like. Whitacre and Barrera (1944) reported that the incidence of amenorrhea among the women in the Santo Tomas Internment Camp in Manila, Philippine Islands, was quite high but especially so among the Army nurses who had gone through the campaigns of Bataan and Corregidor. More serious causes are the acute infectious diseases, or such chronic affections as tuberculosis, diabetes mellitus, the deficiency and hematologic disturbances. In several psychoneurotic maladies, especially anorexia nervosa, these disturbances in menstruation may be present, and they occur at times in hypothyroidism and regularly as one of the presenting signs of several of the classical endocrinopathies. That some cases, otherwise unexplainable, are due to ovarian and anterior pituitary hormonal imbalances is nowadays accepted teaching, but the true hormonal regulation of bleeding has not yet been completely elucidated. Of course pelvic tumors, malformations, or inflammatory disturbances can appear in the causative role.

THERAPY

Actually, the mere absence of menstruation is in itself nothing to be greatly agitated about. Oftentimes the beginning of satisfactory sexual life establishes or reestablishes the flow, but many women have gone into marriage while amenorrheic and have become pregnant all the same. However, the occurrence of one of these menstrual irregularities which is not patently due to a transiently disturbing element in the patient's life should probably be accepted as a signal for a thorough study directed toward the unearthing of one of the underlying maladies listed above. The treatment then becomes the treatment of the primary disturbance. Otherwise, that is to say if all examinations reveal a completely healthy woman who simply is not menstruating often enough or sufficiently to satisfy her or her mother or grandmother, one thing that can be done with considerable hope of success is to administer thyroid substance as in hypothyroidism. Why it should be effective no one knows, but specialists in endocrinology still rely heavily upon it despite the lure of the sex hormones.

In a series of 25 cases of delayed menstruation in women who had had a normal menstrual history up to the last period, Soskin *et al.* (1940) succeeded in each instance in causing the flow to start in an average time of twenty-eight hours by the administration of prostigmine methylsulfate; with one exception all the patients reported normal menstruation at their next regular period.

The dosage ranged from 1 to 3 intramuscular injections of 1 or 2 cc. of the drug in 1:2000 solution. Soskin goes so far as to say that if a woman fails to menstruate after the use of this drug, pregnancy may be diagnosed as accurately as with the Friedman test; Winter (1940) could not confirm this position since the test failed in one of his 4 cases; however, it succeeded in the 6 cases of Cherniack and Sheps (1941) and in 94.5 per cent of the ninety cases of Friedmann (1944).

As to therapy with the sex hormones, the following is the plan suggested by Smith (1944), Professor of Gynecology at the Harvard Medical School: give 1 mg. of diethylstilbestrol orally daily with breakfast for thirty-five days, and 10 mg. of progesterone intramuscularly daily for the following five days. It is said that two to five days after the last injection, a two- to five-day flow will probably ensue. Then, counting the beginning of this flow as the first day, give 0.5 mg. of progesterone intramuscularly daily from the twenty-first through the twenty-fifth day. It is said that a period will then probably occur around the twenty-eighth day. The last two steps are repeated twice, and then again twice, but reducing the diethylstilbestrol to 0.3 mg. daily. After the next period, the usual course of diethylstilbestrol is given daily but the progesterone is omitted; it is said that by that time a spontaneous flow may occur and recur at regular intervals on 0.3 mg. of diethylstilbestrol, taken daily except during flowing, but that if there is no flow by the thirtieth day the progesterone series should be resumed again. Smith says that if after one or more trials with the above schedule of treatment no spontaneity of flow is discernible it is reasonable to assume that the patient has some basic irremediable defect and that nothing further is to be gained with this therapy. Turner *et al.* (1943) have successfully substituted sodium estrone sulfate milligram for milligram for diethylstilbestrol. There do not lack observers, however, who question the justification for such estrogen therapy as the above: (*a*) Fluhmann (1944), of Stanford Medical School, says that the employment of estrogenic hormones (diethylstilbestrol) for most cases of functional amenorrhea is not based on sound physiologic principles, since the amenorrhea usually results from deficient ovarian function and this hormone cannot stimulate the gonads; he admits that uterine bleeding may be produced easily but believes that this is an abnormal flow which does not necessarily recur in a month following cessation of treatment; (*b*) Abarbanel *et al.* (1943) felt that the principal indication for diethylstilbestrol was as an aid to offset the physical and psychic maladjustments that might occur, and that if the syndrome is functional in origin a well-balanced properly cooked diet combined with a judicious use of thyroid over the space of many months was of much greater importance; (*c*) Novak (1943) felt that the inadequacies of diethylstilbestrol in the treatment of amenorrhea need to be stressed. As for progesterone, normal menstrual cycles followed for a variable period of time in only one third of Allen and Soule's (1943) twenty-three cases. Hamblen (1942), surveying the whole subject of progesterone therapy, said there was at least at that time ample evidence that the therapeutic role of progesterone was yet to be delineated clearly.

Reidenberg (1943) said that restoration of normal menstrual function occurred in 71 per cent of 51 amenorrheal women and in 78 per cent of 37 oligomenorrheal women following low dosage irradiation of the pituitary gland and the ovaries; not all observers, however, are convinced of the harmlessness of this procedure.

MENORRHAGIA AND METRORRHAGIA

(Dysfunctional Uterine Bleeding)

The first of these terms means prolonged or profuse flow, and the second, flow at irregular intervals between the periods, but they can probably be satisfactorily designated here by the single term, excessive bleeding. Sometimes such bleeding occurs just as a girl reaches maturity and does not recur, but it may take place at any time during, or even after, a woman's menstrual life. In most of the latter, postmenopausal, instances the cause is a neoplastic growth, but the fact is not to be overlooked that such growths may occur and cause excessive bleeding in younger women also. Other conditions giving rise to bleeding, which is usually slight and of the "spotty" kind peculiar to older women, are senile endometritis and vaginitis. In younger women the causes are most frequently found among the following: tubal pregnancy, threatened abortion, retained gestational products, retrodisplacement, ovarian cyst, uterine fibroids or polyps, endometrial hyperplasia, pelvic inflammatory disease. Excessive bleeding may occur in either hypo- or hyperthyroidism and is seen in some of the other classical endocrinopathies. Likewise it probably occurs as a reflection of some of the less understood pituitary-ovarian imbalances. Congestive heart failure, hypertension, leukemia, hemophilia, thrombocytopenic purpura, the acute infectious diseases—Danforth (1935) includes even syphilis—may be partially manifested in excessive bleeding.

THERAPY

I think it obvious that therapy must be directed by diagnosis made through a process of exclusion, and that these matters, most of which are gynecologic, cannot be presented in this book. Of course bleeding after the termination of the menstrual life always calls for bimanual and speculum examinations and sometimes diagnostic curettage as well. In young girls bleeding excessively for their first few periods, rest in bed, an ice-bag to the lower abdomen, and ergot are time-tried remedies. The last is probably more successful since ergonovine has become available; the drug may be given intramuscularly or even intravenously in a dose of 0.2 mg. (1/320 grain) in emergencies, or it may be given by mouth several times daily for several days. As in scant or no bleeding, so in these cases of excessive bleeding, thyroid substance is often of value; Foster and Thornton (1939) relieved 12 of their 13 patients with metrorrhagia and 6 of their 7 with menorrhagia. Smith (1944) says that doses approaching tolerance may sometimes have to be given. It is rare for a patient who is not a youngster to escape successive dilatation-curettages. The men of my time in hospital were given to understand that a diagnostic curettage is one thing and a therapeutic one quite another, but attitudes seem to have changed radically in this matter, for nowadays many men who would not attempt other radical surgery seem to feel competent to perform this neat little operation. Of course I am not qualified to pass upon such things.

As for sex hormone therapy, Smith (1944), Professor of Gynecology at Harvard Medical School, advises as follows: To those who bleed regularly but too profusely or too long, give 10 mg. of progesterone and 1 mg. of estradiol intramuscularly on the twenty-first day and follow on the twenty-second to the twenty-fifth day by 10 mg. of progesterone intramuscularly. He says that three cycles of this therapy are usually sufficient. For those whose periods are occurring too frequently the same procedure is used, beginning the injections

eight days before the anticipated onset of flow and continuing until the cycle lengthens. For those having continuous flowing, Smith advises the immediate intramuscular injection of 10 mg. of progesterone and 1 mg. of estradiol and then of 10 mg. of progesterone daily for the next four days. He says that during this time the bleeding will probably decrease or cease and that two to four days later a fairly normal period will occur. Counting the beginning of this period as the first day, he would have the injections repeated beginning on the twenty-first day. Treatment of this sort he says should be given at least twice and that it may be required again after a lapse. He says that if the patient is bleeding profusely, the daily dose of progesterone may even be raised to 50 mg. for a time. Cuyler, Hamblen and Davis (1942) employ diethylstilbestrol by mouth in daily doses ranging from 2 to 6 mg. in place of the estradiol; others have since used diethylstilbestrol with satisfaction. Instead of estradiol, Cuyler *et al.* (1942), and this same group of Hamblen's at Duke University in 1943, substituted the oral administration of diethylstilbestrol or of sodium estrone sulfate, either apparently being satisfactory in a dosage range from 2.5 to 12.5 mg. daily. Rubenstein (1943) felt that cases could be separated into two groups by employment of the vaginal smear technic, progesterone being given to those in whom a highly cornified vaginal smear indicates hyperplastic endometrium and estrogen to those whose smear resembles that of a normal prepubertal girl. Testosterone seems in many instances undoubtedly capable of checking dysfunctional bleeding, but most observers feel that its use is contraindicated since it may lead to the development of male characteristics, hirsutism, atrophy of the breast and change of voice. Karnaky (1943) observed a case in which these changes were not reversed upon the cessation of treatment.

Low dosage irradiation of the pituitary gland and ovaries was successfully employed in about half of Reidenberg's (1943) thirty-seven cases; however, despite Kaplan's (1943) report of a young woman who became pregnant and gave birth to a normal child after roentgen therapy of the splenic and pituitary regions, many men do not feel certain that this type of treatment is entirely safe—Te Linde, in discussing Kaplan's paper, said that he had seen some tragic permanent amenorrheas caused in young women in this way and that he does not use irradiation in women under thirty-five years of age.

Biskind *et al.* (1944) said that evidences of nutritional deficiency are to be found in a large proportion of these patients and that prompt improvement in the gynecologic condition often follows upon the administration of vitamin B complex orally or parenterally (see Index for methods). Gubner and Ungerleider (1944) employed vitamin K in an attempt to stop the excessive bleeding in the belief that impaired hepatic function is a contributory factor in the genesis of various menstrual disorders; it will take a great deal of work, however, to justify this viewpoint.

ESSENTIAL DYSMENORRHEA

(Painful Menstruation)

Perhaps more than 50 per cent of women suffer from dysmenorrhea, the symptoms varying from a mild physical and mental discomfort to severe attacks of pain that wrack the patient's back, head, legs and lower abdomen for several days and leave her in a state of great fatigue during the early part

of the intermenstrual period. Grant that dysmenorrhea is only a symptom and not a disease, and classify the various types on an alleged causative basis, the fact will remain that there is a constitutional something underlying all the cases; that is to say, that the dysmenorrheic woman differs in some essential way from the nondysmenorrheic. This position is of course challenged, and the attempt is made to find a neuralgic, ovarian, congestive, obstructive, inflammatory, mechanical, autonomic, endocrine, or allergic cause in all cases—which would be very fine were it not for the fact that the very same *causes* are found in many individuals who do not have dysmenorrhea. Therefore, in the present state of our knowledge, the term "essential dysmenorrhea" would seem still to be permissible.

THERAPY

Surgical Measures.—Various surgical measures from bilateral ovarian denervation or presacral sympathectomy to hysterectomy are employed, of which perhaps the soundest theoretically is dilatation of the cervix in the attempt to convert the nulliparous uterus into a condition similar to that of the parous uterus, it being noteworthy that women who have suffered from dysmenorrhea frequently no longer do so after they have borne a child. This dilatation, however, oftentimes gives only temporary relief, in which cases the use of pessaries is advised in the hope of prolonging the asymptomatic period—a practice that many physicians look upon as vicious. It is also claimed that if the internal os is severed in addition to the dilatation, the percentage of permanent cures is greatly increased. This may be true, but since most of these patients will not consent to operation (even were it advisable to urge it, which is questionable), the method is of relatively little use. Carbon dioxide insufflation of the fallopian tubes has been advocated, but not all of those who have employed it have found it effective.

I believe that all but a relatively few enthusiastic gynecologists have given up the routine suspension of retroverted uteri, a truly heinous anatomical abnormality that has at one time or another been held responsible for all of the ailments of the daughters of Eve.

Exercise.—Miller, in 1934, seemed to have convinced himself by careful study that faulty posture has nothing to do with dysmenorrhea, but in 1940 he expressed the opinion, which is certainly shared by many, that much benefit is often to be derived from prescribed exercises, especially in young women. The system of simple exercises, which Clow described in 1932, follows. (Of course these exercises are to be prescribed only for women otherwise healthy.)

Hygiene.—There is no reason why the patient should not bathe as usual except that the tub bath may be esthetically objectionable. The shower or sponge bath is still available, however, and if taken quite hot is often very helpful.

Intranasal Therapy.—The question of the interrelationship between the nose and the female generative organs was first raised by Fliess, in 1897, and in the years immediately succeeding gave rise to a considerable controversy among German otolaryngologists and gynecologists. The "genital spots" in the nose are the tuberculum septi (prominences on the upper anterior part of the nasal septum on each side) and the anterior portion of the inferior turbinate on each side. It is claimed that at menstruation these areas swell, become sensitive and bleed easily. It would seem that treatment of these areas deserves some consideration, for Crossen, in 1926, collected the reports of 81 cases

treated by three physicians, with success in 63 cases, or 77 per cent. The method probably is laughed at too much and tried too little.

Method.—Apply 20 per cent solution of cocaine to the genital spots during the height of the pains; if they cease, the case is likely to respond favorably to the treatment, which aims at permanent ablation of these spots and is instituted between periods. This consists of the application of trichloracetic acid to the spots four times at intervals of about five days, allowing time between treatments for the disappearance of the slough that forms. The applications are painful and may be preceded by cocainization.

Sedatives, Analgesics and Antispasmodics.—It is the rare and fortunate case that responds to the sedatives alone; these drugs are discussed under Insomnia. Likewise, it is unusual for a patient with severe dysmenorrhea to obtain complete relief from analgesics, but many patients do have the worst edge taken off their pain by them. Those most frequently used are acetanilid, 3 grains (0.2 Gm.), acetphenetidin, 5 grains (0.3 Gm.), and acetylsalicylic acid,

TABLE OF EXERCISES FOR HEALTHY DYSMENORRHEIC WOMEN

1. *Floor Polishing.* Kneel on "all fours." Swing right arm with elbow stiff, through a semicircle, as if polishing the floor, reaching as far forward and as far back as possible. Repeat swing ten times with each arm.
2. (*a*) *Bending.* Stand with feet apart. Stretch arms above head, bend forward and touch ground with knees straight. Return to first position. Repeat slowly eight times.
   (*b*) *Twisting.* Stand with feet apart. Stretch arms to side on level with shoulders. Twist trunk round until right arm points directly backward. Twist again until left arm points directly backward. Repeat vigorously ten times.
   (*c*) *Swaying.* Stand with feet apart. Stretch arms above head. Sway body and arms to right then left. Repeat slowly ten times.
3. "*Rowing.*" Sit on floor with knees straight and feet pressed against wall. Lean forward and touch wall with knuckles, allowing knees to bend slightly. Repeat rhythmically twenty times.
4. *Right to Left and Left to Right.* Stand with feet apart. Swing right arm up as far as possible. Bend down bringing right arm over and touch left foot. Repeat six times. The same with the left arm and right foot.
5. *Floor Patting.* Kneel, sitting back on heels. Twist body and tap floor with both hands four times on left side. Kneel upright. Twist body and repeat tapping on right side. Repeat eight times each side.
6. *Bean Picking.* Throw 20 small objects, such as beans, on the floor. Pick up one at a time and place on a shelf above the head using hands alternately. Do it as quickly as possible.

5 grains (0.3 Gm.); caffeine citrate, 2 grains (0.12 Gm.), combined with either of these sometimes enhances its power, though of course it may cause sleeplessness in some individuals. The above drugs should be given every three to four hours, beginning the day before the attack is expected. Amidopyrine in 5-grain (0.3 Gm.) dosage is probably better than any of them, but its tendency to cause agranulocytosis should cause it to be withheld in any case in which hematologic studies cannot be made—a drastic statement, but probably justified by the evidence.

Alcohol is the analgesic par excellence in dysmenorrhea, as many patients know without being so instructed by the physician. I believe that there are plenty of women capable of taking alcohol in small amounts and at long intervals as a medicine. That the gynecologist fears this type of therapy more than does the general practitioner is probably due to the fact that the gynecologist, like all other specialists, knows his patient too little to have a valid opinion of her stability.

Opium will of course relieve this pain, but its use is very dangerous because of the great likelihood of inducing the habit. There are some cases, however, in which respite can be obtained by no other agent. Codeine is preferable to morphine or dilaudid; the ½-grain (0.03 Gm.) dose twice a day, or the ¼-grain (0.015 Gm.) dose at shorter intervals, is less completely analgesic than the stronger drugs but it is also less constipative, less nauseant and less depressant to the general metabolism. The danger of codeine habituation is practically nil.

In 1911, Novak of Vienna, being struck by the fact that many women with increased irritability of the autonomic nervous system suffer with dysmenorrhea, began the treatment of the condition by the oral administration of atropine, Drenkhahn having been applying the drug directly in the cervical canal for a number of years. In the experience of most physicians who continue to use the drug—and nearly all do, for there is occasionally a strikingly good result—the colicky pains are much more relieved than are the backache, bearing down in the lower abdomen, lassitude, etc. Ordinarily, 1/100 grain (0.0006 Gm.) is given three times daily, beginning two days before expected onset and continuing until the second or third day of menstruation.

The following prescription combines a sedative, ½ grain (0.03 Gm.) of phenobarbital, a member of the belladonna group of antispasmodics, extract of hyoscyamus, ⅚ grain (0.05 Gm.), and an analgesic, acetanilid, 3 grains (0.2 Gm.); the patient should begin the use of these capsules one day before the onset of the period is expected.

℞	Phenobarbital	gr. vi	0.4
	Extract of hyoscyamus	gr. vi	0.4
	Acetanilid	gr. xxxvi	2.3
	Make 12 capsules.		
	Label: 1 capsule every four hours. Not to exceed 4 doses daily.		

Davis (1941) stated that the following drugs are employed in mixture at the Chicago Lying-In Hospital: camphor monobromate, ½ grain; atropine sulfate, 1/500 grain; papaverine hydrochloride, ¼ grain; phenacetin, 3 grains; acetylsalicylic acid, 3 grains. One might write such a prescription as the following:

℞	Camphor monobromate	gr. vi	0.4
	Atropine sulfate	gr. 1/40	0.0015
	Papaverine hydrochloride	gr. iii	0.2
	Acetphenetidin (phenacetin)	gr. xxxvi	2.3
	Acetylsalicylic acid (aspirin)	gr. xxxvi	2.3
	Make 12 capsules.		
	Label: 1 capsule every four hours. Not to exceed 4 doses daily.		

Latterly, benzedrine sulfate has been enjoying some vogue. In the experience of Hundley *et al.* (1939) relief was obtained by the administration of ⅙ grain (10 mg.) in 61 per cent of 186 cases, an additional 14 per cent being relieved by taking a second 10-mg. tablet. In Taylor's (1941) experience with 34 cases, 40 per cent obtained complete relief and 40 per cent moderate relief; the dosage used was 5 to 20 mg. a day. In Larkin's (1941) study of 159 cases through a period of six months the drug proved beneficial in mild dysmenorrhea only. One should not overlook the fact that benzedrine may apparently become a drug of addiction; furthermore it causes insomnia in many individuals, occasionally also arrhythmias are induced or accentuated.

Miscellaneous Agents.—*Thyroid substance:* This agent, used as in hypothyroidism, is frequently helpful. In Foster and Thornton's (1939) 25 cases, the drug effected complete relief in 17 and partial relief in 5; in Shute's (1940) series of 130 cases it was effective far more often than any other agent or measure, bringing about "cure" in 58 cases. One should not be reckless in the use of thyroid substance, however, because dysmenorrhea is not unknown in patients with a slight hyperthyroid tendency and there exists at least the theoretical possibility of exaggerating this state. *Insulin and calcium:* Altschul (1936) and Schrick (1939) obtained good relief in a large proportion of their small series of cases with insulin; Schrick gave 5 units of regular insulin daily before lunch for three to five days before each menstrual period. Boynton and Hartley (1934) said that 33 of their 49 patients treated with calcium were greatly benefited. I should think it would take a very large series of cases with proper controls to show that the diversion and the psychic effects of these agents are not their only valuable properties. *Hypnosis:* Kroger and Freed (1943) obtained complete relief in seven of their nine patients through the use of hypnosis either by itself or with hypno-analysis and age-regression. Obviously this is a measure to be undertaken only by the specialized psychiatrist, but since it aims at raising the pain threshold directly or through eliciting of psychogenic factors indirectly causing the pain, it would seem to be a rational approach since Haman (1944) found the average pain threshold of a dysmenorrheic woman lower than that of nondysmenorrheic women, the study having been performed on a large enough group of subjects to make it of apparent significance.

Sex Hormones.—Smith (1944) of Harvard, whose recommendations for sex hormone therapy in other menstrual disturbances I have freely cited, offered a program of treatment for dysmenorrhea too, but I think it is highly significant that he prefaced it by saying that temporary relief has been obtained with trials of all the available sex hormones with results that have been unpredictable and not consistently confirmable. Hirst *et al.* (1942), of Hamblen's group at Duke, employed estrogenic therapy and obtained a complete absence of pain in 25 per cent and marked relief in 60 per cent of the cycles studied, and after cessation of therapy there was complete absence in 5 per cent and marked relief in 28 per cent of the cycles studied. These results do not seem very impressive to me considering the variability of the phenomena in dysmenorrhea. Boynton and Winther (1942) performed a very interesting and well-controlled study in 100 dysmenorrheic women, 50 of whom were given estriol and the other 50 placebo tablets indistinguishable from the estriol tablets. The difference in the amount of relief obtained in the two groups was so slight that the authors felt their findings showed the need for careful controls in the evaluation of therapeutic measures in an entity having as many psychogenic factors as does dysmenorrhea. Randall and Odell (1943) also made this latter point very strongly and said that in their opinion the use of estrogens may even be possibly dangerous. In fairness it should perhaps be pointed out, however, that the drug used by Boynton and Winther has not proved very satisfactory as an estrogenic agent in any studies of which I am aware.

Testosterone has been reported to have been favorably used a number of times; a recent report is that of Jacoby and Rabbiner (1943) who obtained relief in 4 and improvement in 8 of their 18 patients, but this is considered by many observers to be a dangerous agent to use (see Menorrhagia).

PERIODIC INTERMENSTRUAL PAIN

Some women experience discomfort, malaise and uni- or bilateral intermittent pelvic pain of colicky nature and variable degree precisely halfway between their menstrual periods. At the present time this syndrome is variously attributed to uterine contractions, peristalsis of the tube or tubes, ovulation, distention or rupture of an ovarian cyst. The whole operative gamut has been run in these cases, but it is difficult to see how any therapy, other than the use of sedatives and analgesics if necessary, could be really justified in the present state of our knowledge. However, there do not lack men who would have testosterone used in these cases; this is certainly not conservative therapy. Smith (1944) says that thyroid substance is the simplest medication; it is certainly the safest.

PREMENSTRUAL TENSION

Several years ago Frank used the term "premenstrual tension" to describe a syndrome occurring in the premenstrual phase a week or so preceding the menstrual flow and terminating sharply with the appearance of that flow. The most usual symptoms are headache, emotional instability, irritability, abdominal distention, nausea and vomiting, increased sex desire, pruritus and swelling of the vulva. In some instances the symptoms are severe in degree and the psychic alterations in particular may pose serious problems for the family of the sufferer.

THERAPY

Greenhill and Freed (1941) approached this malady as a disturbance in electrolyte and water balance and treated it with ammonium chloride to prevent the retention of sodium in the tissues. The drug was given in 15 grain (1 Gm.) doses three times daily, starting ten to twelve days before the expected period, and the patient was asked to refrain from using table salt or sodium bicarbonate preparations during the treatment. Definite relief was obtained in 34 of the 40 patients.

Rubenstein (1942) reported 6 interesting cases in which the principal symptom was terrific headache that was unrelieved by any of the usual remedial agents. The patients were all high strung active women of the child-bearing age whose premenstrual vaginal smears were indicative of a relatively atrophic vaginal mucosa. Prompt amelioration of the symptoms was said to occur in each of these cases when 1 mg. of estradiol was injected intramuscularly about a week before the onset of menstruation. Smith (1944) indicated that he uses 0.2 to 0.3 mg. of diethylstilbestrol orally with breakfast daily throughout the cycle in cases of premenstrual tension; Rubenstein (1942) used this agent in somewhat smaller dosage successfully in some of his cases.

Freed (1945) found that most of his group of 60 patients obtained definite relief following treatment with testosterone. Thirty of the patients received injections of 10 to 25 mg. of testosterone propionate, depending upon the severity of the symptoms, on the tenth and third days preceding the expected menses; the other 30 were given methyl testosterone by mouth in 10 mg. dosage daily starting ten to seven days before the expected onset. It was thought that the oral therapy was more effective than the parenteral; in one

patient given the drug by mouth nausea was experienced, and in those who received it parenterally menstruation was occasionally delayed but otherwise there were no untoward reactions.

Biskind *et al.* (1944), who feel that several of the menstrual disturbances are associated with vitamin deficiencies, have in some instances obtained relief of their patients through administration of the vitamin B complex.

PERIODIC MASTALGIA

The fact that in some instances of premenstrual tension the only disturbing symptom has been painful breasts during the premenstrum has led some observers to classify this condition as a separate entity. Smith (1944) says that the simplest remedy in these cases is diethylstilbestrol, 0.3 mg. daily, reduced to 0.2 mg. daily as soon as relief is experienced, but he most emphatically warns that such therapy is to be restricted to those whose breasts are engorged, thickened or diffusely nodular, the presence of a discrete mass, cystic disease, or bloody secretion of course calling for thorough study of the local situation. However, Fluhmann (1944) advises that judgment be reserved with regard to these agents since good results have been reported following the employment of ridiculously small amounts of them and even from the use of biologically inert ovarian substance. Testosterone has also been used in some of these cases of mastalgia, but again it seems necessary to repeat that most men do not look upon the use of this agent as a conservative measure.

THE MENOPAUSE

At the period in their lives when involution of the ovaries takes place, which occurs usually between the forty-fifth and fiftieth years, women pass through the climacteric state, of which either sudden or gradual disappearance of menstruation is the invariable and most outstanding manifestation. In about 16 per cent of women, indeed, it is the only manifestation save for the atrophy of the breasts (often masked by deposition of fat), uterus and external genitalia, which occurs more or less gradually during several succeeding years and is often but not invariably accompanied by some diminution in sexual desire and a slight alteration toward masculinity, and obesity. In an additional 4 per cent of women the only other symptom noted is slight "flushing." But in the remaining 80 per cent one or more of the following are experienced in variable degree: hot flushes, characterized by sudden dilatation of the skin vessels, sweating, and a sensation of suffocation often succeeded by a feeling of cold; precordial pain, palpitation, and high blood pressure; arthritic pains; paresthesias, tinnitus, vertigo, headache, insomnia; emotional instability, mental clumsiness, hypochondriasis and depression with suicidal tendency.

THERAPY

This is not a disease but rather a natural transition in her life which every woman must experience. As a matter of fact, as Novak (1940) pointed out, there are not a few women to whom the climacteric comes as a sort of boon,

women who are transformed from a thin scrawny state after years of child-bearing and domestic worry into a plumper, serene type of matron, a sort of second flowering. To be sure, some are disturbed much more than others and really suffer severe physical discomfort and mental disquiet, but we in medicine have as yet no magic wands at whose waving these things are invariably caused to pass. In the vast majority of instances with a moderate amount of disturbance, the sedatives remain the best drugs. Thyroid extract is of value in patients tending toward the hypothyroid state. Sympathetic and understanding treatment in her home is to be fostered for the patient by acquainting the family with the nature of the disturbances and the extent to which their helpfulness will be of real assistance to her. A hobby, or anything that will prevent introspection, is to be encouraged. Travel, if it can be afforded, is sometimes desirable, but on the other hand it may be harmful to a woman who will worry over the conduct of her home while she is away. The fear of cancer should be dispelled, by repeated examinations if necessary. Under the head of "estrogen therapy" below, I have attempted to present what may be currently expected from this type of treatment.

Estrogen Therapy.—In the use of this term I mean the employment in therapy of the estrogenic substances obtained from pregnant human or mare's urine, the estrogenic substances as a whole available for oral, intramuscular, or suppository administration (amniotin, follacro, menformon, and the preparations of some drug houses which are merely described as estrogenic substances); estrone available for oral, intramuscular and suppository administration and for topical application (menformon, ovocylin, progynon); estradiol available for oral and intramuscular administration (ovocylin, menformon, progynon); and the synthetic preparations with hormone-like action, diethylstilbestrol (stilbestrol), dihydrostilbestrol (hexestrol), and octofollin.

Indications and Results.—Of course those who are making a special study of sex hormone therapy in the menopause are justifiably using these preparations a great deal, but for the general practitioner the fact cannot be too often reiterated that even among the small minority of women whose symptoms at the climacteric are severe enough to compel them to consult a physician there is a large proportion who are not likely to profit by estrogen therapy. For example, of 100 women admitted to the Boston Dispensary endocrine clinic because of severe menopausal symptoms, Lawrence and Moulyn (1941) found a positive test for prolan in the urine in only 48. In 81 per cent of this positive group the symptoms were preponderantly those of vasomotor instability, which was, to be sure, definitely benefited by estrogen therapy in 90 per cent of instances. However, in the other 52 patients, whose test for urine prolan was negative, treatment with these preparations caused improvement in only 25 per cent, whereas simple psychotherapy or sedation brought relief in over 80 per cent. Abarbanel *et al.* (1943) also controlled about 50 per cent of their more than 400 menopausal patients without resort to estrogen therapy.

The classical peripheral circulatory changes, the hot flushes, headaches, asthenia and insomnia, seem to be the symptoms favorably affected with greatest regularity. Shorr (1940), who has contributed so much to the subject through the development of a vaginal smear test for objective evidence of response to treatment, has found that patients differ markedly in their sensitiveness to estrogen therapy—in about one fourth of his patients symptomatic relief occurred with relatively little change in the vaginal smear; in about one half relief was experienced at intermediate levels of vaginal change; and with

the remainder complete relief was not obtained until full replacement and a follicular smear were achieved. If psychoneurotic symptoms in a woman in the climacteric persist after the altered vaginal smear indicates complete estrogenic replacement, it becomes easier to accept these symptoms as arising from causes other than the menopause. Sevringhaus (1941) has pointed out however that with regard to symptomatic response as a whole there are often variations in the results from day to day in a given patient. Observers disagree regarding the effect upon hypertension; Shorr, however, found that well stabilized hypertensions were scarcely or not at all affected in his series but those associated with emotional instability tended to stabilize at lower levels under estrogen therapy. Apparently some slight increase in libido is hoped for more often than it is achieved. The arthralgias may persist very severely despite most intensive estrogen treatment. Cohen *et al.* (1940) alleged that the benefits are striking but "of a general systemic nature," whatever that may mean. It seems to me significant that leaders in the study of the arthritides *per se*, such as Cecil (1939) and Hench (1939), have been much disappointed in their results with this type of therapy. A number of observers have reported favorable responses to estrogen therapy in cases of involutional melancholia, but Ripley *et al.* (1940), of Shorr's group, were quite pessimistic. Heaver (1940) felt that experience has conclusively demonstrated that the stimulation resulting from estrogenic therapy may seriously aggravate the psychosis; he would not have the estrogenic substances employed in even severely neurotic, to say nothing of mildly or profoundly psychotic, patients. The fact should never be overlooked that the menopause may be all that is needed to precipitate a psychotic reaction that has been for a long time latent. Indeed, it seems that one of the most discouraging things in this type of treatment is the fact that an apparently satisfactory adjustment all along the line may be completely upset by the advent of a new psychic strain.

Choice of Preparation.—I believe it is the consensus that equivalent results can be obtained with all of the estrogenic preparations provided suitable dosage adjustment is made. However, diethylstilbestrol has been by far the most extensively employed of these agents because of its relative cheapness and greater degree of effectiveness when given by the convenient oral route.

Dosage.—The wide variations in response from patient to patient, above discussed, together with the fact that there is as yet no general agreement as to what amount of symptomatic relief should really be sought, make it at present impossible to state anything like a standardized dosage of these preparations, particularly the natural estrogens. However, as regards diethylstilbestrol, there seems now to be general agreement with Novak's (1944) statement that only rarely is a larger daily dose than 0.1 mg. needed. Abarbanel *et al.* (1943), as the result of an experience in a large number of patients, advised initial daily dosage by mouth of 0.1 to 0.25 mg. and that only enough of the drug to last two weeks should be prescribed. Then, depending upon the patient's response, the dose level may be maintained or increased by doubling the initial quantity. The patient should then be seen at two-week intervals and the dose level adjusted until she is in good equilibrium; *i.e.*, she is having no flushes at night and only an occasional one during the day. Abarbanel *et al.* maintain the dosage required to achieve equilibrium for a month or so before beginning gradually to lower it, attempting to keep the patient at equilibrium for a minimum of three to six months before discontinuing use of the drug. Under this regimen satisfactory relief was secured in over 92 per cent of their cases.

Danger of Inducing Cancer.—It has been demonstrated that under certain conditions in the experimental animal the administration of estrogenic substances is capable of inducing the appearance of carcinoma. Whether this is also true in women under treatment with these substances is of course a question of utmost importance. Novak (1944) says it is the consensus that no such hazard pertains to clinical employment of estrogens in any customary therapeutic dosage but councils against the employment of treatment in persons who harbor any so-called precancerous lesion or those who have a clearcut family history of cancer. However, Auchincloss and Haagensen (1940), disturbed by the probability that estrogens may have been a contributing cause of the breast cancer which developed in their patient, and calling attention to the fact that the stimulus to breast growth which the estrogens exert is as evident in human beings as in laboratory animals, listed the following circumstances under which they believed these substances should not be used: (*a*) in large or prolonged doses; (*b*) when there is a family history of breast cancer; (*c*) without initial and repeated clinical examination of the breasts; (*d*) in patients with chronic mastitis, carcinoma or any other form of breast neoplasm, either before or after surgical or radiation treatment.

Disagreeable Reactions to Stilbestrol.—In their study of this agent before it was released for commercial distribution, Shorr *et al.* (1939) found that in 80 per cent of their series of 44 patients its use was associated with toxic symptoms in the form of nausea, vomiting, abdominal distress, anorexia, diarrhea, lassitude, paresthesias, vertigo, thirst, an acute psychotic reaction and cutaneous rashes. The toxic effects upon the liver and the blood platelets, which sometimes follow enormous dosage in experimental animals, do not seem to have been observed when the drug is used in the human in the therapeutic dosage range. Novak (1944) says that in his experience the proportion of women in which the drug cannot be used because of disagreeable reaction is only from 10 to 15 per cent, which he believes to be about the average noted by most gynecologists. As a matter of fact, most recent reports are mentioning only gastro-intestinal reactions, which are alleged to subside under adjustment of dosage in nearly all instances. However, Kasselberg (1942) reported a case of exfoliative dermatitis due to diethylstilbestrol, and Novak (1944) has warned of the ease with which the use of the drug can induce postmenopausal uterus bleeding often leading to the clinical suspicion of cancer and not infrequently calling for diagnostic currettage.

OBESITY AND MALNUTRITION

OBESITY

Here I am concerning myself solely with the commonly encountered state of overfatness which is unassociated with any recognizable endocrine dyscrasia. To Newburgh, who has given much thought and study to this matter, the cause of such obesity is simply overeating; indeed, that obese individuals *do* overeat, though they may deny the impeachment, has been shown. For example, Strang and Evans (1930) allowed a group of new patients, who considered themselves small eaters, to take for three or four days exactly what they ordinarily ate at home; 8 of the 13 individuals averaged an intake of 2570 calories, though they were obviously more abstemious than when at home, since they lost an average of 2 pounds each. Kisch's (1937) patients were even more gluttonous: 46 of the 50 consumed food with a value of 2900 to 3500 calories, and 28 of 30 who were fed 200 calories in excess of their basal requirements while lying in bed complained that they were not receiving enough to eat. It would seem that those who argue that obese individuals are not obese because they like food too well are losing their case, for the contention that the overeating is due to a faulty metabolism which requires the excessive storage of water and salts and fats was not substantiated in the metabolic studies of Bruch (1940) and others. However, the belief that there is a strong factor of heredity in obesity dies very hard, but it is a more likely thing that it is a certain type of body build and not obesity itself that is inherited. I recall a case seen in Bauer's clinic in Vienna, a woman who had been elsewhere diagnosed as having pituitary disease but whose "girdle" distribution of fat was found to be common to other members of her family. Bauer expressed the feeling, in 1941, that the adipose tissue of an obese person may differ from that of a normal person in having a greater tendency to accumulate fat, but this viewpoint was certainly not substantiated in the careful experimental study which Block (1942) performed in three obese subjects.

Overweight is a matter deserving serious attention for the following reasons: it predisposes to a number of diseases, particularly diabetes mellitus, gout, cholelithiasis, varicose veins, hypertension and arteriosclerosis; it greatly lowers the resistance against infectious diseases; it greatly increases surgical risk; and it causes considerable inconvenience and even suffering to its victims. It is a strange fact that in all the prehistoric sculptures, and well up into the definitely historical Sumerian and Egyptian periods, the female figure is always shown as grossly obese and the male as slim and athletic. I wonder if the usual explanation of this, *i.e.*, that it indicates the sedentary life of the women of those times, is entirely correct; could it not also be that for reasons almost as inscrutable as those obtaining today the canons of art of the time rigidly proscribed all other depiction?

THERAPY

Principles.—In obesity, in addition to stored water, the bulk of the excess weight consists in stored fat, which can only be got out of the tissues by causing

it to burn. That is to say we must deny food to the patient so that he will live off the surplus in storage. Starvation would be the ideal but for the fact that under such conditions there occurs depression of metabolic activities sufficient to defeat our purpose. The treatment must therefore consist in supplying what one might call a small air draft of food in order to keep the fat fire in a good glow of burning.

TABLE 18.—REDUCTION DIETS AS USED BY NEWBURGH

Four Hundred and Fifty Calorie Diet

Protein 60 Gm., Fat 9 Gm. and Carbohydrate 32 Gm.

	Household Measure	*Weight, Gm.*
Breakfast:		
6 per cent fruit	1 serving	100
Skimmed milk	1 glass	200
Coffee		Ad libitum
Luncheon:		
Meat or fish	2 oz.	60 cooked
3 per cent vegetable	1 serving	100
Skimmed milk	½ glass	100
Dinner:		
Meat or fish	3 oz.	90 cooked
3 per cent vegetable	1 serving	100
Skimmed milk	½ glass	100

Six Hundred Calorie Diet

Protein 65 Gm., Fat 9 Gm. and Carbohydrate 65 Gm.

Breakfast:		
6 per cent fruit	1 serving	100
Bread	1 slice	30
Skimmed milk	½ glass	100
Coffee		Ad libitum
Luncheon:		
Meat or fish	2 oz.	60 cooked
3 per cent vegetable	1 serving	100
6 per cent fruit or vegetable	1 serving	100
Skimmed milk	1 glass	200
Dinner:		
Meat or fish	3 oz.	90 cooked
3 per cent vegetables		
1 raw	1 serving	100
1 cooked	1 serving	100
9 per cent fruit or vegetable	1 serving	100
Whole milk	½ glass	100
Tea or coffee		Ad libitum

Newburgh's Diet.—The feeling has been growing through recent years that attempts to accomplish a slow loss of weight through rather liberal plans of dieting, which have been in vogue in many clinics, have for the most part failed because the patients are so discouraged with the slow loss of weight that they give up the attempt altogether. The tendency nowadays therefore is to revert to dietaries in which the calories are very sharply restricted, and there is no longer any fear that patients on these radical reduction diets will not

maintain nitrogen balance, for Strang and McClugage showed a good many years ago that individuals on diets as low as 450 calories daily will remain in nitrogen balance so long as the protein is held at 60 Gm. Since Newburgh and his associates at the University of Michigan are among the foremost advocates

TABLE 18.—*Continued*

Eight Hundred Calorie Diet

Protein 73 Gm., Fat 28 Gm. and Carbohydrate 65 Gm.

Breakfast:		
6 per cent fruit	1 serving	100
Egg	1	50
Bread	1 slice	30
Butter	1 teaspoon	5
Luncheon:		
Meat or fish	2 oz.	60
3 per cent vegetable	1 serving	100
6 per cent fruit or vegetable	1 serving	100
Skimmed milk	1 glass	200
Butter	1 teaspoon	5
Dinner:		
Meat or fish	3 oz.	90
3 per cent vegetables (1 raw, 1 cooked)	2 servings	200
9 per cent fruit or vegetable	1 serving	100
Skimmed milk	1 glass	200
Butter	1 teaspoon	5

One Thousand Calorie Diet

Protein 75 Gm., Fat 42 Gm. and Carbohydrate 85 Gm.

Breakfast:		
6 per cent fruit	1 serving	100
Egg	1	50
Bread	1 slice	30
Butter	1 teaspoon	5
Coffee ad libitum, with milk	1 oz.	30
Luncheon:		
Lean meat, fish	2 oz.	60
or		
Cottage cheese	3 oz.	90
3 per cent vegetable	1 serving	100
6 per cent fruit or vegetable	1 serving	100
Bread	1 slice	30
Butter	1 teaspoon	5
Whole milk	1 glass	200
Dinner:		
Lean meat or fish	3 oz.	90
3 per cent vegetables (1 raw, 1 cooked)	2 servings	200
9 per cent fruit	1 serving	100
Whole milk	1 glass	200
Tea or coffee		Ad libitum

of radical dieting for reduction in obesity, I am offering here in Table 18 their full reduction diets, necessarily altered here by the omission of sample menus and enhanced by the addition of household measures where they have been omitted. The reader will find food value tables in the article on Diabetes.

Newburgh and his group routinely use the 450 calorie diet. They point out that green leaves and fruits are emphasized in this diet, the bulk thus affording partial compensation for meagerness and also supplying vitamins; however, vitamin B complex is prescribed as a supplement. The skimmed milk supplies nearly 0.5 Gm. of calcium which is sufficient for an adult, and practically all of the protein is of animal origin. Fluid intake is not limited.

Newburgh says that upon a diet of this type the patient will lose from 3 to 5 pounds a week on the average and that he may be assured that he will lose 50 pounds (23 Kg.) in three or four months. It is said that after a few weeks when patients are convinced that they are really losing at the promised rate they find it less trying to continue the plan; however, for those who work hard and cannot continue their occupations unless they get more to eat, the diets of higher caloric value are available. Newburgh finds that often such patients can be satisfied with 600 calories and he only allows the 800 or the 1000 calorie diet when absolutely convinced that it is necessary.

Reducing Diet for Children.—Kerley and Lorenze (1941) reported that all of the 103 children whose dietetic management comprised the employment of the diet schedule shown in Table 19 lost weight; indeed in some instances cited the losses were quite remarkable. The diet was generously supplemented with vitamins A, B, and D.

However, Bronstein *et al.* (1942) reported their inability to effect appreciable losses of weight in their series of children regardless of the type of treatment used, and they emphasized the fact that in their experience over a long period of time obesity in mentally adequate children tended to correct itself at about puberty, at which time the children become cognizant of their obesity as a handicap and are then willing to cooperate satisfactorily in a dietary regimen. Newburgh stresses the point that the treatment of obesity in children must emphasize behavior rather than diet and that it is an integral part of the treatment to teach them to control their whims and desires and to help them develop a sense of proportion. He says that sharp underfeeding may be too great a load when coupled with the correction of behavior and that if the calories of the diet are adjusted through training and selection of food to stop further gain in weight, the obesity will gradually disappear as height increases.

Water.—The most usual custom is perhaps to restrict somewhat the water allowance below that which is normal, but it is doubtful if this serves any very useful purpose provided the patient is not allowed to gorge herself on water during the periods of greatest weight loss. There are physicians, however, who stoutly maintain that water restriction is of great value in that as water is withdrawn from the tissues the other deposited substances are carried with it. The use of diuretics is even sometimes recommended.

Subjective Changes.—Strang's experience accords with that of all who have succeeded in gaining the cooperation of obese individuals sufficiently to obtain results: "One is astonished at the unanimity with which patients reported a return of vigor, a feeling of well-being and resistance to fatigue which had been lost for months or years. A great variety of obscure symptoms and minor ailments disappeared." Headache and difficulty in breathing usually disappear very rapidly, and as a whole the symptomatic improvement exceeds what can be accounted for by the relief from the mechanical burden of only a relatively few pounds. Menstrual disturbances often strikingly improve.

Exercise.—Tennis, golf and horseback riding are favored for those who can afford them. Swimming is very excellent because of the added energy loss

incident to the prolonged cooling of the body surface, but it should be noted that the reducing value of any exercise is lessened as soon as skill is acquired. Bauman advised the daily walking of 2 miles in forty-five minutes or less, or calisthenics lasting ten minutes morning and night; he found that ordinary housework does not replace systematic exercise. Strang and his associates were skeptical of the value of exercise, maintaining that routine calisthenics do not make up for the increased food intake as a result of the stimulation of appetite. They feel that the individuals who most need rapid weight reduction because

TABLE 19.—A REDUCING DIET FOR CHILDREN SUPPLYING BETWEEN 1100 AND 1200 CALORIES AND P 75, F 35, AND C 125

Fruits	All cooked and raw fruits except banana, ½ cup or 4 ounces
Fruit juices	Tomato, orange, or grapefruit, 1 cup or 8 ounces
Eggs	Boiled, poached, or scrambled egg without fat, 1
Cheese	Any variety, 2 ounces
Meats	Poultry, lamb, beef, liver, or fish, 3 to 4 ounces
Vegetables	Spinach, lettuce, celery, tomatoes, string beans, cabbage, Brussels sprouts, chard, cauliflower, broccoli, onion, asparagus, ½ cup at each of two meals
Salads	Any of the above vegetables or fruit served with lemon and mineral oil dressing, ½ cup at each of 2 meals
Desserts	Fruit, gelatin, sherbets, skimmed milk puddings, ½ cup at one meal
Breads	Preferably whole wheat or rye, ½ slice at each meal; Ry-krisp
Beverages	Skimmed milk, not over 1 pint daily; cocoa made with skimmed milk; saccharine to be used as sugar, ¼ grain tablet equalling 1 teaspoon sugar

SAMPLE MENU

Breakfast	*Dinner or Lunch*	*Lunch or Dinner*
1 cup orange juice	3 to 4 oz. lean meat or fish	Cottage cheese on lettuce, 2 oz.
1 egg	½ cup cooked spinach	½ cup asparagus salad
1 glass skimmed milk	½ cup orange and grapefruit	½ cup string beans
½ slice whole-wheat bread	Salad on leaf of lettuce	½ slice bread
	Mineral oil mayonnaise	1 glass skimmed milk
	½ slice bread	½ cup frosted raspberries
	1 glass skimmed milk	
	Lemon sherbet	

of impending exhaustion of the circulatory apparatus after years of chronic strain upon it are the very ones in whom the genuine work necessary to accomplish a real loss of 300 to 400 calories cannot be permitted. Newburgh warns that individuals on a 450 calorie diet may become acidotic if they indulge in much exercise, and he points out that exercise is usually a much harder way of reducing than by limitation of food since, according to his calculations, an individual must walk 36 miles to rid himself of one pound of adipose tissue.

Thyroid Therapy.—The contention that thyroid substance should be given, not in the sense of supplying a deficient internal secretion but rather to

speed up metabolism so that the stored materials can be utilized better when food is withheld, has been attacked by Strang as being irrational if not actually dangerous. Though the basal metabolic rates of his obese patients fell within normal limits for their actual size and weight, they were much above normal if computed upon the basis of ideal weight. For instance a woman, aged forty-one, whose ideal weight was 133 pounds, actually weighed 216 pounds. Her basal metabolic rate was minus 4 in relation to her actual weight but plus 23 in relation to her ideal weight. "In other words this patient as far as her real self, her active useful tissues, was concerned was operating at a level 27 per cent higher than was normal for her." Such levels of metabolism would normally be associated with thyrotoxic symptoms, and if they really supply an index of the increased work being done by the obese in merely living, the further whipping up of the rate with thyroid substance should certainly be approached with full caution. Bulger (1936) made the point that in the obese adolescent especially the drug should not be used, since we do not know "to what extent such tinkering may upset neuroendocrine equilibria." Bruch (1941) stated that in order to obtain a stimulating effect on the metabolism much larger doses are needed than are generally given to obese patients and that the claims for the specific value of thyroid substance in the treatment of an obese child can frequently be discarded on the basis of insufficient dosage alone. Short said he found thyroid not well tolerated in the beginning during the period of increased metabolism, but that it gave consistently good results as the metabolic rate fell under the influence of the reducing diet. However, Andersen (1940) reported in detail 3 cases of very severe thyrotoxicosis in women past the climacteric in which he believed the excessive use of thyroid substance in weight reduction was responsible. Newburgh (1942) said that in his opinion only when the occasional patient is encountered whose basal metabolic rate is pathologically low is thyroid medication justified.

Other Drugs.—Bram (1940) proposed the use of *digitalis* leaves, 1 to 2 grains (0.06 to 0.12 Gm.) three times daily at meals, to reduce the appetite; this seems to me a drastic step to take for digitalis is a very potent agent. Greene (1940) used the tincture of *belladonna*, alone or with a sedative, in a small series of cases, in quite a large proportion of which the appetite was reduced; this is another potentially toxic agent. The most recently proposed agent is *benzedrine sulfate* (*amphetamine*), which is also not only a very potent drug but one to which patients may possibly become addicted. Ersner's (1940) report on this drug was an enthusiastic one because apparently in most of his "more than 500 cases" the loss of appetite consequent upon taking the drug made dieting easy. He offered no records of basal metabolic studies but said these records showed very little change under the drug; in most instances constipation seems to have been induced and often there was a great deal of premenstrual tension, irritability and lightheadedness in the beginning. Ersner began with a single daily dose of 1 tablet of $\frac{1}{6}$ grain (10 mg.) and consumed more than three months in reaching the full dosage of 1 tablet after each meal; the one daily dose was given for the first month, followed by a rest period of a week, then the preceding dosage was given for a week before proceeding to the use of 2 tablets, and the final dosage was reached by the same process. Recent reports of the satisfactory use of this agent are those of Colton *et al.* (1943), Kunstadter and Necheles (1943), Albrecht (1944) and Pelner (1945). Kunstadter and Necheles felt that in addition to depressing hunger the drug improved discipline in their children and enabled them to follow their diet with

greater ease. Albrecht felt that in some respects the drug is too effective an adjunct to the restricted diet; many patients seek its continued use as a "crutch". Colton *et al.* felt that it should be used only as a temporary expedient to facilitate the formation of restricted eating habits, their best results in diminishing appetite having been obtained by the administration of 5 mg. upon arising, 5 mg. at 11 A.M. and 5 mg. at 4 P.M. *Dinitrophenol* should be used under no circumstances whatsoever for there is ample proof of its highly toxic nature.

Contraindications to Drastic Dieting.—These are felt to be the presence of a tuberculous lesion, myocardial disease and advanced cardiovascular-renal disease. Some observers feel that nevertheless some effort should be made in all cases of gross obesity to aid the patient to cope with his major disease by at least gradually reducing his weight. Adolescents and the elderly, who are thought to bear reduction measures poorly, have been dieted very drastically without the occurrence of any untoward incidents.

MALNUTRITION

Malnutrition is seen in individuals who are unable to obtain sufficient nourishing food to prevent semistarvation, in those who suffer from faulty utilization of food as the result of some circumstance such as vomiting, pylorospasm, diarrhea, etc., and in cases of pituitary cachexia, which is an extremely rare condition. In addition there are the cases with which I am dealing here, undernourished individuals who usually fall into one of the following three main types: those who are just "naturally" thin; those who have lost much weight during a period of excessive physical or mental strain or illness and have subsequently failed to regain it; and those girls or young women (occasionally a young boy) with anorexia nervosa, in whom, as well stated by Ryle (1936), "a psychic trauma or a foolish habit or some combination of the two results in a loss of appetite and a suppression of the menses." In all, the difficulty lies in the possession of a subnormal appetite, for it has often been shown that there is nothing at all to prevent these patients from putting on weight if one can only induce them to eat enough.

THERAPY

Stuffing Diet.—The dietary scheme which served Ralli and Brown (1933) well is here given in the form of a table (Table 20). Their patients gained an average of 17 pounds in six weeks on this diet. Once the initial repugnance for excessive amounts of food is mastered, patients usually eat with relish and after a while retain an improved appetite without special effort. Ralli and Brown's patients averaged a daily calorie consumption of 4000 to 4040; the diet provides a total of 5060. But not all patients can be induced or can force themselves with the best of will to cooperate fully in this stuffing campaign.

Egg-yolk Powder.—Steiner (1941) reported 10 patients ill of rheumatoid arthritis or of nephritis, hospitalized for long periods and either not gaining or even losing weight on a well-balanced diet of 2600 to 3000 calories; 9 of the 10 gained an average of nearly 10 pounds during an average period of about eight weeks as a result of adding to the diet daily 100 Gm. of egg-yolk powder,

suspended in milk with vanilla and sugar added to taste. The 100 Gm. of powder were said to supply 67 Gm. of fat, 22 Gm. of protein and 620 calories.

TABLE 20.—DIET FOR THE UNDERNOURISHED PATIENT (RALLI AND BROWN)

	Amount.	C.	P.	F.	Cals.
Breakfast					
Cereal	1 oz.	23	3	0	104
Cream	3⅓ oz.	2	2	20	196
1 glass milk	8 oz.	12	8	9	161
Egg	One	0	6	6	78
Bacon (crisp) strips (use fat for egg)	1 oz.	0	3	19	183
Banana or prunes	3⅓ oz.	20	1	0	84
Orange juice	6⅔ oz.	20	1	0	84
Butter	1 oz.	0	0	25	225
Bread	3 slices	54	9	0	252
Jam or jelly (2 heaping tablespoonfuls)	1 oz.	30	0	0	120
Sugar	8 t.	40	0	0	160
Coffee	1 cup	0	0	0	
		201	33	79	1647
At 10 A.M.					
Cocoa malt with 1 egg and cream or 8 oz. milk with 1 egg and cream	1½ glasses	40	19	36	560
Lunch					
Meat-fish-chicken	3⅓ oz.	0	20	20	260
Potatoes-rice-spaghetti	3⅓ oz.	20	2	0	88
Salad { Mayonnaise	1 T.	0	0	15	135
Salad { 15 per cent fruit—2 lettuce leaves	3⅓ oz.	15	1	0	64
Bread (1-oz. slices) or 1 large roll	2 slices	36	6	0	168
Vegetables, 5 per cent	3⅓ oz.	3	1	0	16
Butter	1 oz.	0	0	25	225
Dessert { Pie, Puddings or custard, Ice cream	3⅓ oz.	20	4	4	132
		134	53	100	1648
At 4 P.M.					
Cocoa malt with 1 egg and cream (½ glass) or 8 oz. milk with 1 egg and cream	1½ glasses	40	19	36	560
Dinner					
Meat (2 oz. cheese or 3 eggs)	3⅓ oz.	0	20	20	260
Potato-rice or a creamed vegetable	3⅓ oz.	20	2	0	88
Butter	½ oz.	0	0	12.5	112
Bread (2 slices, 1 oz. each)	2 slices	36	6	0	168
Vegetables, 10 per cent	3⅓ oz.	6	1	0	28
Dessert (same as noon)	3⅓ oz.	20	4	4	132
		122	57	70.5	1348
Night Meal 10 P.M.					
Vegetables for sand	3⅓ oz.	3	1	0	16
Bread	2 slices	36	6	0	168
Mayonnaise or butter	½ oz.	0	0	8	72
Milk	1 glass	12	8	9	161
		51	15	17	417
or					
Hershey bar (10-cent bar)	One	35.8	5.6	24.5	398
Substitutions					
Noon					
Bread	4 oz.	72	12	0	336
Mayonnaise or butter	1 oz.	0	0	30	270
Meat (ham, salmon or chicken)	3⅓ oz.	0	20	20	260
or	or				
Cheese	2 oz.				
Cocoa malt or egg malted milk	1½ glasses	40	19	36	560
Bananas or 20 per cent fruit	Two	40	2	0	168
		152	53	86	1594
Supper					
French toast					
Bread	3 slices	54	9	0	252
Eggs	2	0	12	12	156
Butter	1 oz.	0	0	25	225
Milk	½ c.	5	3	4	68
Sugar	2 T.	30	0	0	120
Jam or jelly	2 T.	30	0	0	120
Cocoa malt or egg malt milk	1½ glasses	40	19	36	560
		159	43	77	1501

Total calories for all meals 5060.

Insulin.—In a usual dosage of 5 units three times daily, twenty minutes before meals, Higgons and Ostlund (1934) found insulin of value in under-

nourished children who do not respond satisfactorily to the usual hygienic and dietary treatment, but of no value in those already gaining; they found very young children frequently thrown into hypoglycemic shock. Bram (1940) also thought it a valuable agent in children as well as in adults. In Blotner's (1938) series of 100 adults improvement in appetite (some of the patients became voracious eaters) and in the sense of well-being and in physical and nervous strength was a marked early and persistent effect. These patients were all ambulatory and all normal physically except for the moderate to severe malnutrition. They ordinarily injected 10 units of insulin three times daily about twenty minutes before meals, but some took it only twice a day and in a few instances the dose was increased to 20 units two or three times daily. The injections were usually taken for one to three months, the shortest period being two weeks and the longest seven months. Of course a liberal diet was advised. In most cases the weight gain was 3 to 4 pounds per week for the first two or three weeks, but it became less marked with the passage of time and finally remained constant regardless of the continuance of insulin. The average total gains in those who persisted in the treatment for one to four months were 10 to 15 pounds. Blotner found that the majority of this group of patients maintained the increased weight during various follow-up periods, some as long as four to six years. However, in Nichol's (1932) series of 42 patients, 31 maintained their gain for six months or less and only 4 kept it for three or four years.

Some observers have found that by no means the majority of a group of patients on whom they have tried this therapy have responded. Dorst (1938), studying the matter in Cincinnati, found that patients exhibiting a low flat glucose tolerance curve are not infrequently encountered in his clinic. A number of such individuals responded with gain in weight and in sense of well-being when placed on insulin therapy. However, one must always be on guard—Freyberg (1935) felt that such improvement as resulted in his cases came from the *suggestion* accompanying the insulin injections, but Greco *et al.* (1942) substituted physiologic saline for insulin and said that all of their patients soon complained of lack of appetite. I have not yet seen the report of a satisfactory controlled study of insulin therapy in malnutrition.

Special Features in Anorexia Nervosa.—*Psychotherapy.*—The principles may be summarized from Pardee's (1941) excellent presentation, as follows: (*a*) Separate from parents and while in hospital explain thoroughly the father and mother relationship as well as patient's own emotional drive toward sex and the ego. (*b*) Try to effect realization of the ways in which the patient's failure to meet the issues of life brought on the illness. (*c*) Prove to the patient that she has no organic disease and that the ingestion of particular articles or quantities of food is no more harmful than others. (*d*) Do not attempt to induce feeding by coercion.

Danger of Edema.—In some desperate cases, in spite of the preceding injunction, forced duodenal feeding is necessary as a life-saving measure, and dextrose-saline solution may be given intravenously also for the patient is often dehydrated. It is well, however, to heed Evans and Shulman's (1940) warning against too free administration of salt and water in cases of malnutrition in which there is likely to be a state of relative hypoproteinemia; massive water logging of the extravascular tissues, including pulmonary edema, can suddenly supervene in such cases.

Thyroid Substance.—Some observers have felt that thyroid therapy should

be tried in the hope that the speeding up of metabolism would be accompanied by increase in appetite, while others have held that it is more likely to retard weight increase than to prove beneficial. Richardson (1939) reported a case in which its use was accompanied by an alarming acceleration in the loss of weight. Berkman (1943) felt that thyroid substance should not be used, first because the condition is not the result of a disturbance of the thyroid gland, and second because it may cause retardation in the initial weight gain and a very adverse psychological effect; he says that since 1938 the agent has been rarely used in the treatment of anorexia nervosa at the Mayo Clinic.

Vitamins.—McCullagh and Tupper (1940) said they routinely add vitamin preparations by mouth and have recently been using thiamine hydrochloride (B_1) and liver extract intramuscularly.

Special Features in the Thin Youngster.—Summarizing Bram (1940), the therapeutic approach should be the following: (*a*) Attempt to retrain the stomach to receive and digest food by feeding small quantities many times throughout the day until the eating habit is reestablished. (*b*) Psychotherapy is important. Less blame and more praise from the parents, and a simple unpatronizing explanation of calories, nutrition and health from the physician, are the most helpful approaches. (*c*) Enforce improvement in sleep habits; *i.e.*, stress that hours spent in the bedroom should actually be hours in bed and asleep. (*d*) Supplementary vitamins and hematinics will be indicated in some cases. Bile salts, 3 to 5 grains (0.2 to 0.3 Gm.) at mealtime, sometimes increase appetite and reduce flatulence. Insulin is often useful.

DISEASES OF THE GASTRO-INTESTINAL TRACT

STOMATITIS

Herpetic Stomatitis.—The studies in recent years of Black (1938), Dodd *et al.* (1938), Woodburne (1941) and Scott and Steigman (1941) make it imperative now to recognize as a single entity an acute infectious gingivostomatitis which is caused by the virus of herpes simplex and embraces the maladies formerly separately recognized as catarrhal, aphthous and ulcerative stomatitis. In the primary attack, usually in infants and young children, the clinical picture is usually characterized by systemic infection with fever and irritability, and by soreness of the mouth, red swollen gums, oral fetor and regional lymphadenopathy. In some cases none, in others a few, and in still others many diffuse small ulcerations may appear anywhere in the mouth. In most instances the constitutional symptoms disappear in a few days but the oral lesions often persist for some days or a week longer. According to this new conception of the disease the well-known "canker sore" of children or adults, which occurs without other involvement in the mouth and without constitutional symptoms, would merely be evidence of recurrent local attacks of this virus in individuals who had already won constitutional resistance through the primary attack.

The primary attacks of herpetic stomatitis tend to occur in family outbreaks and among people who are malnourished, though to be sure no direct relationship of this malady to undernutrition has been traced.

Recently, Buddingh and Dodd (1944) described a stomatitis often accompanied by diarrhea and caused by a virus not identical with that of herpes simplex. This disease occurs most frequently in infants under 6 months of age but it has been found to occur sporadically in adults, and it is thought that perhaps such persons may serve as sources of infection for susceptible infants. Adults have also been found to harbor and spread the virus when they themselves demonstrated no evidence of infection with it.

One should remember that pemphigus, erythema multiforme, dermatitis herpetiformis, lupus erythematosus and lichen planus sometimes appear in the mouth. It is thought that in a few cases electrogalvanism from dissimilar metallic dentures has caused oral ulceration.

Gangrenous Stomatitis (Cancrum Oris; Noma).—This type of stomatitis is very horrible, but fortunately occurs rarely and then almost exclusively in young children who have been debilitated by a severe bout of illness; a few institutional epidemics have been reported, however, and Eckstein (1940), having gone to Turkey from Germany, to his surprise saw many cases there; there are also evidences in the literature that this malady is seen not infrequently in the Far East. Beginning as a small ulcer on the mucous membrane of the cheek, lip, or gum, a spreading gangrene rapidly destroys a large portion of one side of the face; death nearly always results in from one to five days. The alleged causative role of the Vincent organism in these cases has never been proved; perhaps some of them are really atypical fulminating agranulocytosis. Eckstein felt that noma is probably a toxic form of severe herpetic (ulcerative) stomatitis.

Parasitic Stomatitis (Thrush).—This malady, which is caused usually by the hyphomycete, *Oidium albicans*, more rarely by a number of other and quite dissimilar fungi, occurs sporadically and sometimes epidemically among nursing infants. It is generally considered to be due to contamination from imperfectly sterilized nursing bottles or nipples, from the introduction of unsterile cleansing solutions into the mouth, and from the mothers' breasts or from the hands of attendants. Premature, weak, athreptic infants, or those suffering from other infectious diseases, are especially predisposed to thrush, but it may also attack otherwise healthy infants. The lesions consist of small gray-white or yellow-brown patches, somewhat resembling milk curds, scattered over the cheeks, gums, lips and tongue; their removal, which is difficult, leaves a slightly bleeding area. Examination of one of these crushed "curds" reveals the organism. The attack usually clears up in two or three days, but hospitals fear thrush because an epidemic not infrequently fails to yield even to vigorous treatment, and without treatment may run a course of several weeks. A few cases of generalized cutaneous monilial infection have been reported and very rarely generalized systemic invasion occurs. MacGregor and Henderson (1943) reported two cases of intestinal thrush in young infants, both of whom died.

Mercurial Stomatitis.—The first symptoms are metallic taste and soreness of the teeth upon chewing; then the gums become spongy, swollen and tender, and they bleed very easily; the breath is quite foul and the salivary glands are swollen and tender. In extreme cases ulceration, loss of teeth, and even necrosis of the bone may take place.

Bismuth Stomatitis.—This type of stomatitis is characterized by a blue-black line along the margin of the gums, soreness of the gums, salivation, and in severe cases ulceration.

Vincent's Angina.—See among the Infectious Diseases.

THERAPY

Herpetic Stomatitis.—During the attack, the soft foods, such as milk, slightly cooked eggs, soups, custards, and the like, are the only foods that adults can take with any sort of comfort; the feeding of infants sometimes becomes quite a difficult problem. Local treatment consists in the use of mouth washes such as the following: tincture of myrrh, 1 part to 25 or 50 parts of water; potassium permanganate, 1 part to 8000 parts of water; or some such mixture as the following, which is a very satisfactory mouth wash:

℞	Thymol (saturated solution)	℥ij	64.0
	Hydrogen peroxide	℥ij	64.0
	Glycerin	℥ij	64.0
	Potassium chlorate (saturated solution) to make	℥viij	250.0
	Label: Dilute and use as mouth wash.		

In infants, who cannot of course gargle or rinse the mouth, it is necessary to apply these washes on a cotton swab. The saturated solution of boric acid has long enjoyed a reputation as the ideal mild mouth wash, a reputation entirely undeserved for the reason that it is practically worthless as an antiseptic.

In recurrent "canker sores" the silver nitrate stick is very effective. It should be firmly applied to the bottom and sides of each of the ulcers, rinsing the mouth with water afterward if the caustic and metallic taste is very objectionable. In more diffusely ulcerated cases the use of potassium chlorate to be

swallowed is recommended by several physicians of wide experience, despite the well-known ability of this drug to cause methemoglobin production; it is excreted partially through the salivary glands and thus the ulcerated surfaces in the mouth are continuously bathed in a potassium chlorate solution. Bradbury states that the drug is almost a specific when used internally. He recommends for an adult 10 grains (0.65 Gm.) three times a day, to be taken well diluted; for a child of six years, 3 grains (0.2 Gm.) every four hours. Wise and Parkhurst recommend 20 grains (1.3 Gm.) three times daily for the adult.

In recurrent cases, Woodburne (1941) successfully employed the repeated vaccination method of treatment: smallpox vaccination is performed at intervals of one to two weeks unless a "take" occurs in which case the reaction is allowed to subside before vaccination is again performed; in Woodburne's series vaccination was performed twice in 3 cases, three times in 2, four times in 5, five times in 4, six times in 2, seven times in 2, eight times in 3, fifteen times in 1. Grace (1943) also reported greater improvement in two recurrent cases, in one of which vaccination was performed twelve times and in the other six times.

Gangrenous Stomatitis.—Very rarely early and radical excision of the gangrenous area without consideration of the cosmetic effect will stop the process; fuming nitric acid and actual cautery have practically no successes to their credit. Tauber and Goldman's (1936) case in an adult progressed rapidly to a fatal termination despite the use of neoarsphenamine systemically (fusospirillary organisms had been found in the lesion) and the following agents used locally: sodium perborate, hydrogen peroxide, potassium permanganate, mapharsen, sodium ricinoleate solution, bismuth pastes and benzoyl peroxide powder. Tratman (1941) treated 11 cases with 6 cures by a combination of sulfonamide given systemically and 5 per cent solution of gentian violet applied to the thoroughly cleansed lesions for a period of thirty seconds every four hours. Of Eckstein's (1940) 9 patients treated with neoarsphenamine 8 died, but of 21 treated by local injections of "antigangrene serum" into the healthy surrounding tissue, 11 progressed to complete recovery; Eckstein believed the action of the serum to be nonspecific. McMillen (1941) reported 7 cases that were astonishingly arrested by the daily application of full-strength formalin; neither sulfanilamide nor sulfapyridine proved useful in these cases.

Parasitic Stomatitis.—Nothing new has developed in the treatment of thrush in a good many years. Faber and Clark (1927), in a careful report of an epidemic in newborn infants, wrote as follows:

"The treatment of a patient who has thrush may follow one of two lines: simple cleansing or the use of antiseptics. For the first, alkaline, but not too alkaline, solutions frequently applied to the mouth may result in cure after a week or two, especially in healthy infants and in infants with mildly virulent strains of *Oidium* [2 per cent sodium bicarbonate solution—H.B.]. The outcome of such treatment is, however, always problematic, and against relatively virulent strains such as we have often seen, is practically certain to be disappointing. Boric acid is not only valueless, but, as the recent experience in Chicago demonstrated, dangerous. We emphasize the point because a recent text in a book on pediatrics recommends the Escherich boric acid sac or teat. This is a small sac of silk or batiste filled with boric acid powder sweetened with saccharin which is placed and left in the infant's mouth, presumably

until the thrush is cured. It is possible that boric acid poisoning might result from such treatment. Solution of liquor formaldehyde has never given us satisfactory results, and we believe that the reason is its poor penetration and its rapid dilution by the secretions of the mouth below the point of disinfecting efficiency [1 per cent solution of formalin is usually used—H.B.]. With mercurochrome-220-soluble we have obtained occasional but not constant retrogression of the oral lesions [1 to 2 per cent aqueous solution—Faber and Dickey (1925)]. With gentian violet we have obtained better and more constant results than with any other substance. To obtain them, however, it is necessary to follow certain rules. Treatment should be given at least one hour after feeding. The mouth should be gently cleansed with several cotton swabs to remove the adherent mucus over the affected areas —a most important precaution, since as Churchman has shown, the dye is absorbed and its therapeutic effect on the lesion annulled by overlying secretion. The dye, in 1 per cent aqueous solution, must be freshly prepared (not more than a few days old) and must be applied generously, first to the affected area and then over the tongue and in the buccogingival folds. The treatment must be repeated once or twice daily for at least three successive days, and, if possible, every other day thereafter for from one to two weeks. The mother's breasts should be carefully cleansed with soap and water before each nursing, and the first few drops of milk discarded to prevent reinfection.

"If this technic is followed, the lesions will have nearly disappeared by the second day and entirely so by the third; new ones will not appear. If only one or two treatments are given, recurrences will frequently occur, usually in other areas than the site of the original lesion. In spite of the deep staining of the entire oral cavity, which persists for a day or two after treatment has been stopped, there is no apparent interference with the baby's appetite or ability to feed. Stain on the lips or chin can be easily removed with a little alcohol. The stools during treatment often appear purplish."

Quite a number of years ago Abraham's (1926) 33 patients were said to have responded favorably to the application of a solution of 2.5 to 3.5 per cent ferric chloride in an average period of from two to four days; higher concentrations were said to have produced irritating effects. Animal experiments showed that the virulence of the organism was considerably decreased by this treatment. I have not seen mention of the employment of ferric chloride in the more recent literature.

Mercurial Stomatitis.—This type of stomatitis is infrequent in the patient whose oral hygiene is perfect unless ordinary therapeutic doses of the mercurials are exceeded. After the teeth and gums have been put in as good condition as possible, it is well to employ the potassium chlorate mouth wash (see Herpetic Stomatitis, above) as a routine practice throughout the period in which the mercury is being given. At the appearance of the first sign of stomatitis the drug should be stopped and then only very carefully resumed upon its subsidence. When the stomatitis is only a part of the general picture of mercury poisoning, one must resort to other measures as well (see Mercuric Chloride Poisoning).

Bismuth Stomatitis.—See under Syphilis.

Vincent's Angina.—The therapy of Vincent's angina (fusospirillosis or trench mouth) is extensively presented under the title Vincent's Angina in the section on the infectious diseases (see Index).

DYSPEPSIA

(*Indigestion*)

It is mandatory upon the physician to approach the diagnosis and treatment of every case of dyspepsia by the purely eliminative process, for though it is undeniably true that the majority of digestive complaints are due to either sensory, secretory, or motor disturbances, and are therefore functional rather than organic in origin, yet the gravity of the organic lesions when present is so great that they must all be ruled out before the diagnosis of a purely functional dyspepsia is accepted. Granting, then, that this has been done, *i.e.*, that the patient has been shown not to have gastritis, peptic ulcer, or cancer, the functional disturbances remain to be considered—provided that two further possibilities are also eliminated, namely, dyspepsia due to dietary indiscretion, and secondary, so-called "reflex" dyspepsia. *Dietary indiscretion* is usually encountered in those of a fulsome habit, who have regard neither for the quantity nor the quality of their food and drink, and who disdain all the decencies of table deportment; occasionally, however, an individual suffering from this type of indigestion will not be one of the gobblers but merely a person who suffers from the taking of small and even well-masticated quantities of certain foods, such as fried and greasy dishes, heavy hot breads, excessively hot or cold dishes, etc. Any of the symptoms of indigestion may be manifested, and they will all usually disappear if the offending articles are withheld from the diet, or if the individual is made to curb his gluttony—that is to say, if a silk purse is made out of a sow's ear. *Reflex dyspepsia* may indicate the presence of gallbladder disease, chronic appendicitis, peritoneal adhesions, epigastric hernia, intestinal worms, cirrhosis of the liver, etc. It should always be borne in mind, as well, that degenerative diseases of the blood vessels may give rise to gastro-intestinal symptoms of either an acute or chronic nature, and that a functional dyspepsia is often associated with disease of the genito-urinary organs, hyperthyroidism, the anemias and pulmonary tuberculosis.

NERVOUS INDIGESTION

This type of dyspepsia, whose sufferers are legion, is characterized by the following facts: the gastro-intestinal syndrome changes frequently, so that at one time the picture will be dominated by a symptom of one sort and at another time by a symptom of another sort altogether; there are usually other psychasthenic complaints, such as palpitation, poor circulation, fatigue, peculiar forms of headache, and the like; there is no definite relationship between the quantity or quality of food taken and the type and degree of the gastro-intestinal disturbances; and the symptoms are very dependent upon the state of mind of the individual at the time he partakes of a given meal. The most usual complaints are of fulness and discomfort in the epigastrium, pain, eructation of gas, nausea, vomiting and difficulty in swallowing. Often the appetite is poor, but sometimes a patient, believing that only by forcing himself to eat will he get well, is given to inordinate performances at table. Others attempt to treat themselves by eliminating articles one after another from the diet in the hope of finding the offending food; such individuals not infrequently maintain themselves in a condition of semistarvation, and affect their malady not in the least unless it be to make it worse.

Psychotherapy.—I quote from Alvarez' excellent treatise on this subject: "The first and often the most important step in the psychic treatment is taken

when the physician makes a complete and careful physical, roentgenologic and laboratory examination. If this does not reveal signs of serious disease, many persons immediately lose interest in their symptoms and go away satisfied. Another important factor in the psychic treatment is the taking of a good history, and especially a history that brings out all the details of family and business worries, of domestic infelicity or of the phobias that so often are at the bottom of the trouble. Unless these things are done, it is not only useless but often criminal to tell the patient not to worry. Some consult us simply because they have been shocked by the sudden death of a friend or relative. They fear that they too have cancer or heart disease, but they will not admit it, and come complaining of some minor ailment. Especially when dealing with older patients, it is often well to say at the close of the examination: 'As we examined you we had always in mind the possibility of cancer beginning somewhere, and we are now glad to say that nothing suspicious has been found.'

"Fortunately, much can be done in many of these cases by giving the patient the mental purgation that comes with the pouring out of secret worries into a sympathetic ear. The physician can often help these persons by advising them wisely, and by leading them out of a maze of muddled thought to the point where they can forgive and forget and acquiesce to things that cannot be cured. For years I have kept in my office a copy of Trudeau's autobiography with a bookmark at page 318 in order that I may turn quickly to his remark that he had learned from his patients that 'the conquest of Fate is not by struggling against it, nor by trying to escape from it, but by acquiescence.' The asthenic person, the person with mucous colitis, or the one to whom nature has given a 'raw deal' can often be made over into a useful and happy member of society if he can be taught this lesson of acquiescence: to stop looking for a cure and instead to settle down to get along as best he can with his handicap.

"The next thing in most cases is to see how a rest can be obtained with the least expense and loss of income. If a vacation is taken, it must be one that will bring the patient back better off than when he left. Too often our vacations are of the type that caused the Irishman to remark plaintively, 'How happy we'd be if it weren't for our pleasures.' If a man cannot well leave his business, he can often, for a month or two, answer his mail and confer with his assistants in the mornings, and can then spend his afternoons at home or on the golf course. I have seen such excellent results from this type of resting that for business men I prefer it to a complete vacation. The mother with several small children and few resources can also be helped tremendously if she is taught to go back to bed after the children are sent off to school. She may have to continue with mending and sewing, but even so, a few weeks of mornings in bed will often work a miracle.

"The sick who are so situated that they must either keep at work or starve can often be taught to hoard their small stock of energy and to live within the limits of their nervous strength. Many tire themselves out by putting too much energy and emotion into trivial tasks. Women in particular must be exhorted to break themselves of the habit of getting all stirred up over little things, and of reviewing at great length painful or annoying experiences which a more sensible person would promptly forget. Others must be taught to go to bed earlier at night and some must for a time retire from leadership or active participation in church, civic, or social work. Some can get their grip again if they will only rest in bed on Saturday afternoons and Sundays."

Oftentimes the physician overlooks the importance of relieving insomnia,

which can frequently be done by teaching the patient to keep his mind off disturbing thoughts, to avoid mental work or exciting conversation after dinner, to take a warm bath and a little food on retiring, and to go to bed earlier. When these measures fail, Alvarez does not hesitate to use the barbiturates, believing that the opposition of many physicians to sleep-producing "dope" is entirely unjustified. The subject of insomnia is separately discussed in a later chapter.

Physical Therapy.—Again Alvarez: "Many of the weak and partly bedridden patients can be put on their feet literally and figuratively only with the help of an intelligent, cheerful and masterful physical therapist who can build their strength until they can stay up all day. Each day the invalid is given something to do, something to think about, something to hope for and some one with whom to talk. Not all persons, however, are helped by massage. Only those 'pussycats' who love to be stroked will thrive on it; those who are ticklish or who hate to be touched by strangers will be made worse. Stoutly built men who were once athletic but who have since become flabby and fat can often be helped by a course with a trainer. Ultraviolet radiation, in my experience, helps in raising resistance, improving appetite and putting on weight.

"These physical therapeutic measures are invaluable in many cases if only because they keep the patient busy and hopeful and bring him back repeatedly under the influence and guidance of the physical therapist and the physician. They keep him out of mischief and out of the hands of the quacks. One of our biggest mistakes in medicine today is that we have allowed others to monopolize these modes of treatment. One of the great advantages of having the work done under our supervision is that we can be watching the patient, learning more about his troubles, and seeing him on occasions when he has something definite and telltale to show us, like a fever, a point of tenderness, or a tinge of jaundice."

Smooth Diet.—Alvarez feels that the most important dietetic considerations are that the patient be taught to eat again, that the diets provided for him be neither too restricted nor monotonous, and that the taking of all unnecessary roughage be forbidden. The virtues of the smooth diet he believes to lie not in the fact that cellulose is so indigestible and by its presence likely to interfere with the action of digestive ferments on starches and other foods, but rather in the assumed existence in the sick individual of areas of reversed peristalsis which fluids will pass but solids will not. To resort in the majority of cases to a milk diet he believes to be unfortunate because milk disagrees with many persons and is bulky and leaves a large residue. If the use of a smooth diet does not bring relief in a few weeks, the case is believed to be one that is not going to be relieved by any form of dietary restriction.

The following are the "smooth diet" instructions often given to patients:

"If you are to give this diet a fair trial, eat no coarse foods with fiber, skins, seeds or gristle. Avoid particularly salads with celery, tomatoes, cucumbers and pineapple, many of the green vegetables, raisins, berries, jams full of seeds, nuts, and many of the raw fruits. Beans, cabbage, onions, green or red peppers, melons, cucumbers, and peanuts are notoriously gassy. If you are living in a boarding house you can stick to this diet by simply avoiding the forbidden foods and eating more of the digestible ones which are put before you.

"Avoid sugar in concentrated form and take no candy or other food between meals. Hot cakes and waffles might not be bad if they were not eaten with so much syrup. Fried foods are not bad if they are properly fried, that is, totally immersed in fat at the right temperature. Avoid eating when in a rush and when mentally upset. Family rows should be held away from the table. Chewing gum may cause distress, as much air is swallowed with the

saliva. Digestion is greatly helped by a good chewing surface. If there are any gaps in your teeth have your dentist fill them with bridges. Purgatives often cause flatulence and distress in the abdomen.

"The following are suggestions for breakfast: Orange juice, grapefruit (avoid the fiber in the compartments); cantaloupes and melons are inadvisable. Coffee, if desired, is allowed in moderation; it sometimes causes flatulence. If you are sensitive to caffeine try kaffee hag or instant postum. Chocolate, cocoa or tea, one or two eggs with ham or bacon (avoid the tougher part of the bacon), white bread, toast or zwieback with butter, any smooth mush such as farina, germea, cream of wheat, cornmeal or rolled oats (a fine oatmeal can be obtained by calling for Robinson's Scotch Groats), puffed cereals and cornflakes are also allowed. Shredded wheat biscuits and other coarse breakfast foods are not allowed. Bran is particularly harmful. Graham bread is permitted but not the coarser whole wheat bread.

"Suggestions for lunch and dinner: In fruit cocktails avoid the pieces of orange and pineapple. Broths, bouillon, cream soups and chowder are allowed, also meat, fish or chicken, squab or game, excepting duck (avoid the fibrous parts and gristle). Veal may be tried; it is not digested well by many persons. Eat no smoked fish or pork. Crab and lobster had better be left alone. Oysters and sausage may be tried later.

"Bread and butter are allowed, and hot biscuits if they are made small so as to consist mainly of crust. Rice, potatoes, mashed, hashed brown or French fried, are allowed; and later may be added sweet potatoes, hominy, tomatoes stewed, strained and thickened with cracker or bread crumbs, well-cooked cauliflower tops with cream sauce, asparagus tips, Brussels sprouts, squash, beets, turnips, creamed spinach, Italian pastes, noodles, macaroni and spaghetti cooked soft, purées of peas, beans, lentils, lima beans or artichoke hearts. All skins or fiber should be removed by passing the food through a ricer. Sweet corn may be used if passed through a colander. There are practically no other vegetables that can be puréed to advantage. String beans (large tender string beans which can be used as a vegetable or salad can now be obtained in cans) are allowed if they are young and tender.

"No salad should be taken at first. Later you may try a little tender lettuce with apples or bananas, tomato jelly or boiled eggs. Mayonnaise and French dressing are allowed. Potato salad without much onion may be tried.

"Suggestions for dessert are: Simple puddings, custards, ice cream, jello, plain cake and canned or stewed fruits, particularly pears and peaches. Cottage cheese is permissible; other cheeses often cause trouble. Apple, peach, apricot, custard and lemon cream pie may be tried if only the filling is eaten.

"In case of constipation, stewed fruit may be taken once or twice a day. In winter the dried pared fruit may be used for stewing. Prunes are probably the most laxative of fruits and if eaten every other morning they will relieve the average case of constipation. They should be cooked slowly until they almost go to pieces. If the skins are still tough they should be discarded. Apple sauce is much more palatable if made from unpared and uncored apples. The sauce is strained later. It may be mixed with a little tapioca or sago. The apples may be baked. Apples, even when cooked, often cause distress. Blackberries and loganberries can be stewed and strained and the sweetened juice thickened with cornstarch. This makes a delicious dish with the full flavor of the berries. Later you may try fully ripe pears and peaches.

"Make no effort to drink water. Be guided by your thirst. Avoid excessive use of salt or other seasoning. If you wish to gain in weight eat as much cream, butter, fat, and starch as you can. If you wish to lose or stay thin, live largely on vegetables, fruits and salads, with a moderate amount of lean meat."

Drugs.—The use of hypnotics has already been discussed. Alvarez believes that those patients who are greatly helped by alkalis will be found to be suffering from ulcer or some other organic disease. He has little faith in tonics and bitters and uses them only at times for psychic effect, in such instances preferring such high-sounding preparations as "beef, iron and wine." Strychnine he looks upon as the last drug on earth to give to a nervous person and shares with most other gastro-enterologists a lack of faith in administered pepsin, pancreatin, etc. Carminatives are sometimes helpful (see Index for prescription).

PYLOROSPASM

Pylorospasm, unassociated with ulcer or other organic lesion, is a spasmodic constriction of the pylorus occurring usually at the height of digestion. Theer

is pain, which may be very intense, eructations and vomiting, sometimes without nausea. A firm protruding mass, indicating the contracted pylorus, may appear in the epigastrium. Vomiting gives great relief, but in many cases the spasms become so frequent that the condition merges into a state of spastic contraction with consequent dilatation of the stomach; the patient can retain no food and of course wastes away rapidly.

Therapy

Read the treatment of nervous indigestion at the beginning of this chapter.

Drugs.—During the attack a hypodermic injection of 1/120 grain (0.0005 Gm.) of atropine sulfate oftentimes gives complete relief, but this drug is not so infallible in its action here as would be expected considering its well-known ability to relax involuntary muscle. Infants are relatively insensitive to it; in pylorospasm, doses of 1/75 to 1/25 grain (0.8–2.4 mg.) are sometimes used in them with good effect and no significant side actions, though it is certainly advisable to make preliminary trial of smaller dosage.

Mackay (1941) reported the cure of the condition in 31, and its improvement in 4 more, of 40 infants given atropine methyl nitrate (eumydrin, a British proprietary not available in this country so far as I am aware); dosage: 0.5 to 1.0 cc. of 1:10,000 solution by mouth twenty to thirty minutes before the six daily feedings per twenty-four hours, increasing 0.5 cc. up to 2.0 to 3.0 cc. per dose, even further increases being made if vomiting was not checked.

In 6 of a group of 16 patients, Beams (1931) obtained relief with the nitrites—amyl nitrite inhaled from the crushed "pearl," or spirits of glyceryl trinitrate (nitroglycerin) 3 drops on the tongue and increasing the dose by 1 drop every two minutes to effect, or sodium nitrite 1 grain (0.06 Gm.) three or four times a day. Eight of the 10 patients who failed to respond to the nitrites responded to atropine given in the form of $\frac{1}{6}$ grain (0.01 Gm.) of extract of belladonna three or four times daily; the equivalent dose in the tincture of belladonna would be about 7 minims (0.45 cc.), in atropine sulfate about 1/400 grain (0.015 mg.).

Myerson and Ritvo (1936) recommended the use of benzedrine sulfate (amphetamine) orally in a dosage of $\frac{1}{6}$ to $\frac{2}{3}$ grain (0.01–0.04 Gm.) in pylorospasm since it has been satisfactorily used to relieve spastic gastro-intestinal states in routine opaque roentgenoscopy. The drug rarely causes more severe reaction than restlessness if not used too frequently, but it should be charily employed in cardiovascular cases. When an opiate is necessary, morphine or dilaudid should not be used for obvious reasons; combine $\frac{1}{2}$ to 1 grain (0.032–0.065 Gm.) of codeine sulfate or phosphate with the atropine.

Dry Diet.—Use of a diet that would be difficult to vomit was advocated by Sauer some years ago. The following case report of Speidel is of great interest:

"Z. C., female, aged twenty-one, came to my office on September 28, 1925, complaining of general abdominal distress, loss of weight, constipation, poor appetite and vomiting. The onset of these symptoms was gradual and began two years previously, about the time she graduated from high school. There was some emotional upset connected with competing for a medal or honors of some sort. All her symptoms had become gradually worse, vomiting occurs now every time she eats or drinks anything. Upon graduating from high school she weighed 92 pounds. Present weight, $69\frac{1}{4}$ pounds. X-ray studies revealed that barium left the stomach very slowly and that there was marked ptosis of both the stomach and large bowel. She was sent to the hospital and for the first week received atropine sulfate 1/150 grain hypodermically after each meal, the regular hospital diet and daily gastric lavage. Under this regimen no improvement occurred. On December 3, 1925, the atropine sulfate was increased

to 1/100 grain after meals, hypodermically, and she was given a dry diet, which in this case meant the regular hospital diet without fluids and without gravies, sauces, soup, fruit juices, and any other liquid or semiliquid food. She was given water half way between meals in whatever quantity she desired. Improvement began at once. On December 11th, the atropine was administered by mouth instead of hypodermically and the dry diet was continued."

Eleven years after this patient first came under observation, Speidel (1936) reported her as still having to adhere rigidly to the dry diet and atropine. But she was otherwise an apparently healthy young woman and had given birth to a normal baby. Interestingly, after delivery she became unable to empty the bladder and obtained permanent relief of this spasm only after mechanical dilatation of the vesical sphincter had been resorted to.

In Infants.—In pyloric stenosis in infants it is usually held that immediate operation is indicated, but Sauer has advised the trial of thick cereal feedings for a time; if the vomiting fails to subside in a week or two and the child does not increase in weight and general condition, operation must be resorted to, and of course it is advised at once when infants are first seen in a very emaciated unresponsive state. It is of interest to note that in Mackay's (1941) series of patients successfully treated with eumydrin (see above) the only ones which did not respond were those which had a high fluid intake. Sauer's mixture is skimmed milk, 9 ounces; water, 12 ounces; farina or rice flour, 6 teaspoonfuls; dextrimaltose, 3 ounces; boil an hour or more in a covered double boiler until thick. From 2 to 6 tablespoonfuls of this is given six to seven times daily, scraped off a narrow tongue depressor well back in the mouth. Fluid is supplied as 6 per cent dextrose in Ringer's solution by rectum. The nutrient enema (see Index) might well be used here; for an infant, 20 cc. of the mixture per hour, slowly injected from an ear syringe. In some instances repeated blood transfusions have been resorted to with good effect; Thompson and Gaisford (1935) believed it inadvisable to give more than 10 cc. of blood per pound in order to avoid undue stress on the infant's heart. After an average time of five to eight weeks, Sauer was able to substitute appreciable amounts of ordinary milk mixtures for a part of the cereal feedings. This nonoperative treatment was effective in 28 of his 35 cases.

Lavage.—In an aged patient in a very poor physical condition Scriver (1931) resorted to the use of the tube and thorough washing out of the stomach twice daily; the patient was saved and became able to retain a diet upon which he gained weight. Subsequent x-ray examination showed disappearance of the previously observed atony. Mackay (1941) obtained no benefit from routine lavage in her series of infants.

HYPERCHLORHYDRIA

This condition, which is more frequent in young and middle-aged persons than in older individuals, is the most common of all gastric disturbances. The symptoms are caused by a more than normal production of acid (*not* an increase in the relative acidity of the juice) during the digestion of a meal, but it should be borne in mind that a gastric analysis which shows an apparently normal acidity does not necessarily rule out hyperchlorhydria, for the reason that the "normal" acidity of the stomach contents during digestion varies widely, and an individual may actually suffer from the symptoms of hyperacidity though an analysis indicates the presence of an amount of acid that is below the "normal" for the majority of persons. The cycle of events is quite characteristic. Pain comes on an hour or more after eating; it is usually of the

mild pressure type but may be very severe and boring and extend into the back and up into the throat. There is heartburn and eructation of acid fluid; occasionally there is also vomiting of very acid stomach contents which burn the throat and mouth. Light and starchy repasts are more prone to produce an attack than are heavier meaty meals. The patients are often otherwise in good health, have a good appetite and are in good flesh.

Therapy

Read the treatment of nervous indigestion at the beginning of this chapter.

The usual remedy for an attack of this kind is to administer sodium bicarbonate in a dose of 15 grains (1 Gm.) when the pain appears and repeat several times if necessary. The large doses often taken by the layman are not necessary and may even induce the production of more acid; and it should be pointed out that the drug is to be taken in warm, but not very hot, water, for the latter converts bicarbonate into carbonate which may in itself be irritating. The reader is urged to turn to the discussion of the various antacids as used in the treatment of peptic ulcer, for what is there said applies equally here.

HYPOCHLORHYDRIA (ACHYLIA GASTRICA)

Vanzant *et al.* (1932), in the examination of 3746 persons, found a steady increase in the incidence of achlorhydria from youth to old age; 23 to 28 per cent of individuals at the age of sixty failed to show free acid on repeated fractional analysis. Polland (1933) confirmed the findings, using histamine to stimulate secretion; Bloomfield (1940) confirmed the earlier workers also, but found that the decline in acidity is not uniform and steady in all individuals. The symptoms of the condition are usually few because gastric digestion in these cases is vicariously performed by the intestine, as shown by Hines (1933). However, there is sometimes loss of appetite and a sense of fulness after eating. Nausea and vomiting are rare. In a few cases there is severe pain, heartburn and eructations just as in hyperacidity; sometimes, too, periods of diarrhea and constipation alternate. Schindler (1940), with his flexible gastroscope, has found some type of gastritis in surprisingly many patients with hypochlorhydria.

Therapy

Read the treatment of nervous indigestion at the beginning of this chapter.

Hydrochloric Acid.—For many years it has been assumed that hydrochloric acid may be expected to act in the following ways in cases of hypochlorhydria: (*a*) as a stomachic, (*b*) to form acid albuminates and so aid in proteolysis, (*c*) to release pepsin from the pepsinogen of the glands, (*d*) to promote an acid medium for the action of pepsin, (*e*) as an antiseptic, (*f*) to stimulate pancreatic secretion and possibly gallbladder emptying, (*g*) to improve tonus and peristalsis, especially that concerned in gastric evacuation, (*h*) to aid in the solution of insoluble calcium and magnesium salts in the ingesta, and (*i*) to stimulate secretion of hydrochloric acid. Koehler and Windsor (1943), studying such of these alleged occurrences as can be simulated by adding acid to a test meal outside the body, have found no evidences that any of these things do take place. Still, since many men continue to administer acid in hypochlorhydria, it seems advisable to continue a description here of the method devised by Dodson a number of years ago:

(*a*) The U.S.P. dilute hydrochloric acid should be given in as large amounts as the patient will tolerate—as much as 2½ drachms (10 cc.) during the digestive period if possible.

(*b*) Instead of employing the continuous sipping method, it is preferable to have acid taken in fractional doses of 30 minims (2 cc.) at a time; one such dose in the middle of the meal and the same amount at fifteen-minute intervals thereafter for an hour or more, lengthening the intervals rather than decreasing the number of doses if unpleasant symptoms arise.

(*c*) Two ounces (60 cc.) of water, grape juice, lemonade, or any other non-alkaline vehicle may be used as diluent for each dose, but the ingestion of other fluids during the meal should be restricted.

(*d*) It may be well to attempt the stimulation of normal acid production by having one meal daily consist almost entirely of carbohydrate, accompanied by the taking of acid as usual. Tests should be performed periodically throughout the treatment to determine whether the secretory mechanism has been reactivated to any degree.

It is well to have the acid taken through a glass tube in order to avoid possible injury to the teeth. Hubbard (1931) found it worth while to use also an alkali-forming diet in patients who show evidences of systemic acid-base imbalance upon prolonged administration of hydrochloric acid. The addition of citrus fruits and green vegetables to the diet will considerably reduce the excessive acidity of the urine.

Lemon Juice.—Bethea and Claunch (1939) reported that 30 cc. of lemon juice in 60 cc. of grapefruit juice (unsweetened), sipped during the latter half of a meal, is often effective therapy. While in the stomach these weak organic acids of course function as acids though they are so metabolized as to increase the alkali reserve after absorption.

Glutamic Acid Hydrochloride.—In combination with hydrochloric acid, glutamic acid forms a white powder which, in contact with water, quickly yields hydrochloric acid. The drug may be given in capsules of 5 grains (0.3 Gm.) with water. Shay and Gershon-Cohen (1936) obtained satisfactory clinical results by the administration of 1 such capsule shortly after the beginning of the meal and another upon its completion, but Wosika (1936) felt that 8 or 9 of the capsules should be taken for best effects. Bastedo (1938) did not find this drug satisfactory.

Digestive Ferments.—In Dobson's studies, the use of the essence of pepsin and the extract of the gastric mucosa, gastron (the dose of either of which is from 1 to 4 drachms), seemed to be without value, since in the absence of acid the enzymes are not effective, and when sufficient acid is placed in the stomach the enzymes appear there. This agrees with the conclusion reached by Bastedo a number of years ago, following a study of the answers to a questionnaire submitted to the members of the American Gastro-Enterological Association: "From this report it is seen that among the members of the American Gastro-Enterological Association many do not prescribe digestive enzymes at all, while those who do employ such enzymes confine their use almost wholly to cases of demonstrated or believed enzyme deficiency. It is further noticeable that almost all who prescribe them show no great enthusiasm over the results of their use, except possibly in the case of pancreatin in proved pancreatic deficiency. The conclusion is therefore inevitable that they are of minor importance in therapeutics."

ATONY

Atony is characterized by a loss of muscular tone, so that the stomach fails to empty itself in the usual time and finally becomes more or less chronically

dilated. The victims of this condition are usually nervous individuals who habitually eat inordinate amounts of difficultly digestible foods and drink large quantities of fluids—until the gastric upset occurs, after which they often attempt to subsist on little more than starvation rations. The most common subjective symptom is a feeling of fulness that appears long before hunger has been satisfied; nausea, eructations, headache, and dizziness also frequently occur, but actual pain and vomiting are rare. A characteristic symptom is that food is tasted long after it is eaten. Gastric analysis shows food remnants seven hours or more after a meal, and on roentgenographic examination the stomach is found to be dilated and its peristaltic action impaired.

Therapy

Read the treatment of nervous indigestion at the beginning of this chapter; indeed, there is little more to do for these patients than attempt to apply that treatment. The diet should be restricted to easily digestible foods to be taken in small amounts six times a day rather than in three large meals. If either hyperacidity or, what is more usual, hypoacidity exists it should be corrected as outlined in the discussion of these two entities. The use of strychnine, so long recommended, has never been shown to have any value.

INTESTINAL FERMENTATION

The patient troubled with intestinal fermentative dyspepsia complains of distention with gas, abdominal discomfort and pain, and the daily passage of several liquid or semisolid stools accompanied by much gas. The stools are quite acid and show evidence of a marked impairment of starch digestion but a quite normal digestion of fats and proteins; at times there is also an overabundance of fermentative organisms present. The patients are usually otherwise in good health, except for the stigmata of neurasthenia, and are not infrequently asymptomatic for long periods.

Therapy

Read the treatment of nervous indigestion at the beginning of this chapter.

Dietetics.—Occasionally these patients are able to identify the particular food which causes their trouble, and when this is eliminated from the diet they remain free from attacks. In practically all cases a radical dietary readjustment is necessary to bring about improvement and cure. The diet suitable under the conditions is one rich in protein and fat and poor in carbohydrate; vegetables rich in cellulose must also be avoided or at least selected with care. In the beginning of treatment, Althausen (1935) permitted his patients to take a little toast or well-cooked cereal but reduced the intake of sugar to a minimum. It is usually considered advisable to exclude the following from the diet: potatoes, rice, root vegetables, dried beans, peas, lentils, cabbage, cauliflower, Brussels sprouts, broccoli, peppers, cucumbers, onions, garlic, pickles, spices and sweet milk. Meat, eggs, fish and cheese, the latter preferably, are allowed. Green vegetables must be cooked and puréed. Cooked fruit, fruit juices, nuts except peanuts, are allowed. There is no restriction of fats. Of course the ultimate aim of treatment is to allow gradually increasing quantities of the prohibited foods until a relatively normal dietary can be resumed.

Lactic Acid.—Althausen, who especially advised the use of buttermilk, often found it necessary to build up tolerance by beginning with small amounts and

working up to a quart a day. He also used lactose at mealtimes, beginning with a teaspoonful and increasing to a tablespoonful. In some instances the attempt is made to overcome excessive fermentation by implanting *Bacillus acidophilus* in the colon; this matter is fully discussed under the treatment of Colon Consciousness.

Kaolin and Charcoal.—These substances are sometimes used to adsorb gases, bacteria and toxins, and to coat the intestinal mucosa.

Intestinal Antiseptics.—The drugs which were formerly called "intestinal antiseptics," salol, betanaphthol, zinc phenosulfonate (zinc sulfocarbonate), and so on, never had any value here, nor is it likely that calomel, so freely taken by individuals suffering from this complaint, is of any worth either. I have not seen the report of any study of the use of sulfaguanidine or sulfasuxadine in these cases, but think it quite unlikely that they would bring relief to these patients.

Carminatives.—The carminative drugs are those which promote the expulsion of gas without in themselves acting as cathartics. They have long been scoffed at by certain therapeutic nihilists, but I believe that many practitioners of long and unprejudiced experience—*i.e.*, the gentlemen who have sponsored more than one empirical remedy that has since been rationalized by scientific experimentation—have considerable faith in their virtues. This group of drugs comprises alcohol, capsicum, cardamom, cloves, ginger, mustard and the volatile oils generally. A very satisfactory carminative prescription is the following:

℞	Tincture of capsicum	ʒss	2.0
	Spirits of peppermint	ʒij	8.0
	Tincture of ginger	℥ij	60.0
	Alcohol to make	℥iv	120.0
	Label: 1 teaspoonful well diluted every half hour until relieved.		

I have heard it said that persons who suffer the sort of gaseous distention which wakes them in the night are often quickly relieved by the taking of bile salts, such as decholin, in doses of 4 to 8 grains (0.25–0.5 Gm.). I do not know how such relief is brought about; but if it is, it is, I suppose.

GASTRITIS

Acute gastritis is a not infrequent accompaniment of the acute infectious diseases and is one of the outstanding symptoms of poisoning with such substances as the metals, alcohol, acids, alkalis. For the management of this condition reference must be had to these subjects as they are discussed elsewhere in the book; chronic gastritis, however, requires to be separately considered.

Chronic gastritis is caused by persistent overeating, by the prolonged ingestion of foods that are digested only with great difficulty, or are taken too hot or too cold, or by the habitual gobbling of all meals; or by the excessive indulgence in tobacco or alcohol, especially the latter; or by the prolonged taking of such drugs as the iodides, copaiba or salicylates. It also occurs as a symptom of ulcer and carcinoma, and may be associated with such diseases as leukemia,

pernicious anemia, nephritis, tuberculosis and other constitutional diseases. It is also nowadays assumed that gastritis underlies hyperchlorhydria and hypochlorhydria, so that these conditions may ultimately lose their clinical identities through being merged in the gastritis syndrome. Heart, kidney and liver affections cause passive congestion of the stomach mucosa and ultimately chronic gastritis. Pathologists who have investigated the matter have felt that, whatever the cause of the condition, there occurs a gradual destruction of the glandular apparatus, though this may be preceded by a period of hyperactivity. However, one must bear in mind that such studies will always be embarrassed by the fact that the normal histologic appearance of the gastric mucosa is none too well known. A very promising approach to the subject is that being made by Schindler and his associates who, as a result of their observations with the flexible gastroscope, are classifying cases into superficial, atrophic and hypertrophic types.

The symptoms are variegated and are such as may occur in any of the dyspepsias. Diagnosis is often difficult, but early morning vomiting of mucus and the finding of large quantities of gastric mucus in the stomach after a test meal, or after a short period of fasting, are very suggestive symptoms, as are also the findings with the gastroscope referred to above.

THERAPY

Diet.—Dietary treatment is essential in these cases. Of course the offending food or drink, if it can be identified, must be absolutely eliminated, and then a very simple dietary regimen must be instituted with the hope of gradually bringing the patient back on to a full and normal diet. Eusterman (1936), of the Mayo Clinic, stated that the smooth diet employed in nervous indigestion, or the dietary regimen of peptic ulcer, is equally acceptable.

Lavage.—Lavage is very helpful, especially in the beginning of treatment. One to 2 teaspoonfuls of sodium bicarbonate to the quart of water should be used and washing persisted in until the fluid comes away absolutely clear; at the end a pint of distilled water should be run in and out. Depending upon the severity of the case, lavage should be practiced morning and evening, or only in the morning, or only two or three times a week. In Hurst's (1934) experience the use of an ounce (30 cc.) of hydrogen peroxide to the pint (500 cc.) of water effectively removed mucus and was sometimes followed by the appearance of free acid in the stomach.

Vitamins, Liver, Ventriculin, Iron.—Eusterman (1939) stressed the point that one must be sure to provide an adequate intake of vitamins, especially A, the B complex, and C, but Shapiro *et al.* (1944) failed to produce any significant changes in the gastric mucosa of five patients treated with a large array of vitamins. Schiff and Goodman (1940) induced marked symptomatic improvement and disappearance of atrophic changes in 5 patients given 30 to 60 Gm. daily of ventriculin (hog stomach extract) together with a bland diet; upon withdrawal of ventriculin in 3 patients, 2 showed return of the atrophic changes and 1 an associated return of symptoms. In a fourth patient atrophic changes returned when taking insufficient ventriculin. The results of Schindler *et al.* (1940), who used liver and iron therapy instead of ventriculin, did not indicate that such replacement therapy might be expected to be specifically curative in all cases of atrophic gastritis. Annis (1944), describing his experience with gastritis in the military service in War II, said he obtained what might be considered good results in only about 20 per cent of instances though he

tried all the accepted measures of treatment including the administration of vitamins and liver.

Acids and Alkalis.—When indicated these agents are used as in hypo- and hyperacidity respectively.

PEPTIC ULCER

(Gastric and Duodenal Ulcer)

Gastric ulcer occurs nearly always at a distance of 2 inches or more from the pylorus; duodenal ulcer is usually located ½ inch or more away from the landmarks which divide the stomach and duodenum; pyloric and primary jejunal ulcers are rare. It is thought that multiple ulceration occurs in between 20 and 30 per cent of cases. Gastric and duodenal ulcers are sufficiently alike in their symptoms and treatment that they may be conveniently discussed under the title "peptic ulcer." Ulcer incidence seems to the clinician to be highest in women between twenty and thirty and in men between thirty and fifty; pathologists (Portis and Jaffe, 1937) raise these figures to thirty and forty, and fifty and sixty, respectively. But there are no absolute age limitations; ulcer may occur in the infant only a few days old or in the centenarian The vast majority of peptic ulcers occur in the duodenum of white males.

The outstanding and characteristic features of peptic ulcer are (*a*) that the patient is usually actively engaged in the affairs of life, has a normal appetite and is not undernourished; (*b*) the history is usually of a chronic gastric disturbance of several years' standing, during which time there have been numerous periods without symptoms; (*c*) there is epigastric pain and tenderness which is extremely variable but not often excruciating and usually not of a radiating type; (*d*) this pain bears a definite relationship to food intake, which was described by Moynihan as follows: "In case of gastric ulcer, the pain which, after an interval, follows the taking of a meal, gradually disappears before the next meal. In cases of duodenal ulcer, the pain continues until the next meal, or until food is taken to give ease to a wearisome pain. The rhythm of gastric ulcer is 'food, comfort, pain, comfort'; and then again 'food, comfort, pain, comfort'; of duodenal ulcer it is 'food, comfort, pain'; and then again 'food, comfort, pain'; a quadruple rhythm in the former disease, a triple rhythm in the latter." The location of the pain to the right or left of the midline is probably of no significance in differentiating between gastric and duodenal ulcer. Posture has usually a definite effect upon the pain. Not all cases of peptic ulcer are so easy to diagnose as this very brief description would seem to indicate; indeed, there are many patients with such a multiplicity of dyspeptic symptoms that diagnosis is extremely difficult; in others, again, nocturnal epigastric pain may be the only symptom. Thanks largely to the indefatigable efforts of the late Russell Carman, who himself suffered the ironic fate of an early death from gastric carcinoma, the x-ray has come to play a prominent part in the diagnosis of peptic ulcer. Gastroscopy has apparently also established its place; Schindler and Arndal (1942) seem to have failed in the differentiation of benign malignant lesions in only 6 of 113 cases of gastric ulcer. The various meals designed to test the motor sufficiency of the stomach also yield valuable information at times. The occult

blood test is a valuable diagnostic aid, for occult blood is present at some time in the feces of the great majority of ulcer patients, but Palmer (1939) made the important differential point that its continued absence speaks strongly for benign ulcer while its continued presence after two or three weeks of treatment strongly suggests carcinoma.

Severe hemorrhage and perforation are the two most feared complications of peptic ulcer. In the exhaustive autopsy studies of Portis and Jaffe (1937), hemorrhage as a cause of death occurred in 18.3 per cent of cases and perforation in 20 per cent. However, these figures only mean that those who died of ulcer died in this way; actually, the total mortality from peptic ulcer is very low—indeed it is now the consensus that a goodly number of peptic ulcers give rise to only very slight and transient symptoms and are therefore never diagnosed at all. The general impression among physicians and surgeons alike that bleeding ulcers do not perforate was not completely confirmed by Winters and Egan's (1939) study of 361 patients with perforation, for bleeding had occurred in 10 per cent of these cases. Studley (1936) contended that if a large loss of weight occurs during the medical treatment of ulcer this also should be counted a major complication, since it greatly increases the hazard of surgical measures which may subsequently become necessary.

In the matter of etiology, practically all students of the disease are agreed that the presence of gastric juice, with its ability to digest devitalized tissue, is of foremost importance since ulcer practically never occurs in the entire absence of acid juice. It is true that Ruffin and Dick (1939) reported achlorhydria in 5.4 per cent of 419 cases of duodenal ulcer and in 6.7 per cent of 42 cases of gastric ulcer, but Palmer and Netter (1940) pointed out the fallacy of basing the diagnosis of achlorhydria upon a single histamine test and further stated that in their own experience with over 2200 cases of proved peptic ulcer no instance of complete and persistent achlorhydria has ever been encountered; witness also the fact that in Kahn's (1937) review of the records of 840 patients with pernicious anemia, and hence achylia, he found not a single case of peptic ulcer. The studies of Berk *et al.* (1942) indicated that the degree of acidity of the stomach contents is by no means the sole determinant of the degree of acidity of the contents of the duodenal bulb, which is the parent site of most clinical ulcers. Palmer, Schindler and Templeton (1938) beautifully demonstrated clinically, roentgenologically and gastroscopically that: (*a*) ulcer is a penetrative process beginning in the mucosa and invading the deeper layers of the gastric wall; (*b*) under favorable conditions healing proceeds rapidly and is so complete that the scar is scarcely visible gastroscopically; (*c*) failure of the lesion to heal may be due to inadequate following of the treatment regimen or to failure of the stomach to empty properly; (*d*) delayed gastric emptying in these cases is frequently attributable to organic or physiologic narrowing of the antrum, failure of the pylorus to open, or both.

As to what it is that permits ulceration to begin in the first place we have still only opinions, which are currently too many and too diverse to justify my listing them here. One fact upon which all observers agree is that the person most prone to develop ulcer is the thin, lantern-jawed, highly strung individual very actively and busily engaged in work, worry and introspection. Rather amazingly, peptic ulcer has emerged as one of the most important medical problems in apparently all of the contending armies in War II.

It has been almost universally held in the past that gastric carcinoma may develop from gastric ulcer, but the occurrence must be very infrequent;

indeed, Hinton and Trubeck (1937) and Palmer (1939) expressed doubt that the transformation ever takes place.

THERAPY

Psychotherapy

Nowadays with the great upsurge of interest in psychosomatic medicine in general, the psychogenic factor in the etiology of peptic ulcer is claiming a great deal of attention. Certainly it is true, as Miller (1944) has so well said, that when the ulcer patient "puts himself in the hands of a competent, sympathetic and understanding physician, transfers to him his personal concern about his condition and cooperates with him in every detail of the management, the first great step toward recovery has been taken." Not all physicians are able easily to establish the ideal relationship between themselves and their patients, but in few conditions is it so essential that an earnest effort be made to do so as in peptic ulcer. It is easy to agree with Miller that in these patients it is of the utmost importance that they see the physician deeply interested in their case and that a definite regimen of treatment is instituted confidently and at once.

Medical versus Surgical Treatment

The old controversy of medical versus surgical treatment has been so thoroughly resolved that Lahey, himself a surgeon, was able to say in 1943: "No one today, I think, can defend primary surgery in the treatment of ulcer. All of our ulcer patients come to us only as medical failures." Internists would not like the term "medical failures," but I think would prefer to say, with justification, that the indications for operation arise essentially from the complications of ulcer. Palmer (1942), who has had vast experience with ulcer, has said that the most frequent indication for operative treatment is cicatricial obstruction (*i.e.*, stenosis), but that even it does not necessarily require operation unless the stenotic lumen is reduced to a diameter of only 3 mm. or less as judged by fluoroscopic study. He of course recognizes acute perforation as a most urgent indication for operation but that subacute and chronic perforations do not necessarily constitute indications. In selected cases of massive hemorrhage he believes that surgical attempts to tie off the bleeding artery or even to excise the lesion may properly be elected, and that in certain instances of recurring massive hemorrhage subtotal gastric resection in an interval between episodes of bleeding may be desirable. Then too, gastric ulcer he believes should be removed if there is serious question as to whether it is benign or malignant, which will of course be the case unless the lesion heals satisfactorily within reasonable time under medical treatment. One might interpolate here that roentgenologists admit their inability to determine whether the lesion is malignant or not in 10 per cent or more of gastric ulcers, and that Walters (1942) said that the clinical symptoms thought to be pathognomonic of benign gastric and duodenal ulcer occurred in a third of the cases of carcinoma in which operation was performed at the Mayo Clinic, temporary effective response to a medical regimen having occurred in 80 per cent of this group; Walters therefore felt that most gastric ulcers should be removed surgically without too much delay. Palmer thought that jejunal ulcer may be treated medically, although as a rule its management is more difficult than that of a primary duodenal or gastric ulcer, and hence operation may be in order in these cases. His list of indications for operation closes with the state-

ment that no medical or surgical procedure, except total gastrectomy, will regularly result in complete and permanent achlorhydria and that hence there is no method of therapy which regularly results in the complete and permanent cure of the disease peptic ulcer.

Bed Rest, Frequent Feeding and Alkalis (Sippy Type of Treatment)

The principle of this treatment is to keep the patient in bed for three to four weeks and to maintain what are considered to be ideal conditions for the healing of the ulcer by the use of frequent small feedings and sufficient alkalis to maintain the gastric juice practically neutral in reaction between 7 A.M. and 10:30 P.M. In cases attended during the first few days by copious secretion during the night, this is removed by aspiration two or three times each night until such time as the amount of juice present in the stomach during the night does not exceed 10 cc.

Diet.—In the beginning, 3 ounces (90 cc.) of equal parts milk and cream are given every hour from 7 A.M. to 7 P.M., eggs and cereals being added after two or three days; by the tenth day the patient is receiving, at three of the feedings during each day, one soft egg and 3 ounces (90 Gm.) of cooked cereal. Thereafter, vegetable purées, and other soft and palatable foods, such as cream soups, jellies, marmalades, custards, etc., may be added; but no feeding should exceed 6 ounces (180 Gm. or cc.), and milk, cream, eggs, cereals and vegetable purées should continue to form the basis of the diet. Lean meat should not be used when it may interfere with tests for occult blood in stools and aspirated stomach contents. It is desirable to have the thin patient gain weight.

The Sippy Alkalis.—Alkalis are given midway between feedings, alternating the following two mixtures: (*a*) 10 grains (0.6 Gm.) each of heavy magnesium oxide and sodium bicarbonate; (*b*) 10 grains (0.6 Gm.) of bismuth subcarbonate or calcium carbonate and 20 to 30 grains (1.2–2 Gm.) of sodium bicarbonate.

Efficacy.—Formerly used almost to the exclusion of all other methods, the Sippy treatment has nowadays been superseded to a considerable extent by the methods subsequently to be described. However, Wosika and Emery (1936) reaffirmed its efficacy in a carefully performed study in a group of 55 patients.

Simultaneous Administration of Milk and Alkali.—The observers just cited above gave powdered milk and alkalis together in one dose at intervals of one hour instead of alternating feedings and dosing with alkali at half-hour intervals as in the classical treatment. More recently, Wosika (1938) reported the substitution of 12.5 Gm. of powdered skimmed milk for 90 cc. of milk and cream. He reduced the amount of sodium bicarbonate from 2 to 0.6 Gm. and increased the amount of calcium carbonate from 0.6 Gm. to 2 Gm. This mixture, given in tablet form once an hour, was said to have resulted in a more complete neutralization of gastric acidity than was possible with the routine Sippy procedure.

Alkalosis Accompanying the Regimen.—According to the accepted standards for an ideal antacid (*i.e.*, that it is insoluble, does not irritate the stomach and intestines, is neutral in aqueous suspension but capable of neutralizing acid, does not unduly alter the acid-base equilibrium in the body, when taken in any reasonable amount will not alkalize the urine with the attendant danger of precipitating crystalline phosphates in the kidney or ureter, will not cause diarrhea or constipation, and will not seriously alter the mineral metabolism), sodium bicarbonate is far from satisfactory. It is soluble in water; it is irri-

tating in high concentrations; it is absorbed and produces alkalosis when taken in excess; and it alkalizes the urine and occasionally causes the precipitation of crystalline phosphates in the pelvis of the kidney, the ureter or bladder. Lockwood and Chamberlin reported several years ago that sodium bicarbonate in about one-half the patients examined caused a rebound in gastric acidity to a point higher than would have been attained had the alkali not been administered. Also of considerable importance is the fact that numerous observers have reported the development of alkalosis in Sippy-treated patients. The symptoms of alkalosis most often noted are headache, aversion to food, dry mouth, excessive thirst, lassitude, nausea and sometimes vomiting; in more than usually severe cases mental deviations may appear, together with muscle and joint cramps, dizziness and tingling in the extremities, and spasmodic movements. With some patients these symptoms appear soon after beginning the alkalis, with others later on. At times they pass away in a few days even though the alkalis are continued in the same amounts, indicating, perhaps, that the organism makes some sort of compensatory adjustment in these cases. Again, the toxic symptoms become so pronounced and persistent that the alkalis have to be stopped for a few days, and sometimes the symptoms return as soon as the alkalis are resumed, so that they have to be abandoned at least in quantities sufficient to neutralize the free hydrochloric acid continuously. In cases with severe vomiting and threatened tetanic convulsions it is necessary, in addition to stopping alkali and food administrations, to give large quantities of physiologic saline solution intravenously to compensate for the chloride losses. Kirsner and Palmer (1943) were able to continue administration of the alkali and overcome the alkalosis in a majority of a small series of patients by simply increasing the sodium chloride intake to 10 Gm. daily. This is a very rational procedure because chlorides are lost from the system in any type of alkalosis even though there is not vomiting. Rafsky *et al.* (1932) reported a successful attempt, in 61 cases with adequate controls, to build up a tolerance for alkalis, as follows: daily doses of 50 grains (3.3 Gm.) sodium bicarbonate, 20 grains (1.3 Gm.) calcium carbonate and 12 grains (0.8 Gm.) magnesium oxide, gradually increased by the end of the second week to 160 grains (10.6 Gm.), 35 grains (2.3 Gm.) and from 12 to 20 grains (0.8–1.3 Gm.), respectively. In absence of clinical or biochemical evidence of alkalosis, the dosage was further increased until there was a complete cessation of symptoms, for which the average maximum dose necessary was 315 grains (21 Gm.) sodium bicarbonate, 60 grains (4 Gm.) calcium carbonate and from 12 to 35 grains (0.8–2.3 Gm.) magnesium oxide.

There have been numerous references to renal damage in alkalosis resulting from the use of alkalis in peptic ulcer. Eisele (1939) felt that the work of the kidneys is greatly increased; he found the urinary excretion of solids nearly doubled. The nitrogenous elements, as well as inorganic phosphates and sulfates, may rise in the blood. Kirsner and Palmer (1941) found it unusual, however, for albumin, casts and red blood cells to appear in the urine, and Kirsner *et al.* (1943) said that the long-continued administration of alkali in man with or without alkalosis does not lead to significant anatomic changes in the kidneys attributable to alkali. With regard to the association of alkali therapy and stone, the evidence is conflicting; Krestchmer and Brown (1939) found that the small incidence of patients who had been treated for ulcer among their 1260 cases of kidney and ureteral stone was not of statistical significance, while Eisele (1940) found the incidence rather high among his 505 cases.

Vitamins.—Archer and Graham (1936), Bourne (1938) and Portnoy and Wilkinson (1938) found patients on ulcer diets often in the subclinical stage of scurvy, which suggests of course the advisability of using adequate amounts of ascorbic acid (vitamin C). Latterly there has been interest also in supplying other vitamins in these cases (see chapter on the Deficiency Diseases for methods).

Substitutes for the Sippy Alkalis.—The neutral antacids, tricalcium phosphate and trimagnesium phosphate, have been tried, usually together in doses of 10 to 25 grains (0.6–1.5 Gm.) each. They do not often adequately serve to neutralize the amount of acid present. Mutch, in England, introduced synthetic hydrated magnesium trisilicate, which has since been satisfactorily used in a dosage of 15 to 30 grains (1 to 2 Gm.), occasionally as high as 60 grains (4 Gm.), by a few men in small series of cases with apparent satisfaction; one advantage claimed for this agent (Mutch, 1937) is that it will not cause alkalosis. Heffner *et al.* (1941) found small amounts of silica excreted in the urine but no evidence of toxicity therefrom.

Kirsner and Palmer (1941) compared antacids in peptic ulcer patients with a technic comprising hourly removal of gastric contents for determination of relative acidity and hourly administration of the alkali. The drugs studied were calcium carbonate, sodium bicarbonate, aluminum hydroxide, tricalsate, tribasic calcium phosphate, magnesium trisilicate, magnesium carbonate and tribasic magnesium phosphate. Calcium carbonate, in dosage of 2 to 4 Gm., and magnesium carbonate, in dosage of 2 Gm., were found to be the most effective neutralizers of gastric acidity.

Steigmann and Fantus (1940) found that a number of "antacids" give symptomatic relief without producing a uniform and constant reduction in gastric acidity, from which they concluded that the relief of pain is secured in a different manner than simply by means of antacid action; Berk *et al.* (1943) shared this viewpoint at least with regard to duodenal ulcer for they found that the reduction of intraduodenal acidity is neither great nor long-lasting and may be followed by a rebound increase. Several observers have recently redirected attention to the fact that the pepsin factor in ulcer has been almost forgotten. Fogelson and Shoch (1944), having demonstrated that a synthetic agent, sodium alkyl sulfate, is capable of markedly inhibiting the peptic activity of gastric juice *in vitro* without causing a significant deviation in *p*H in the acid range, and having obtained excellent results with the drug in experimental ulcers in dogs, tried it out in man. They said that all of their patients had been sent to them by their physicians because they were classified as having "intractable" ulcers and that 26 of the 34 individuals in the group had their symptoms controlled by sodium alkyl sulfate and were so well restored physically that they were accepted by either the armed forces or industry. The dosage employed was 3 grains (0.2 Gm.) every two hours throughout the day. Unfortunately, however, neither Steigmann and Marks (1944), nor Kirsner and Wolff (1944), were able to duplicate these results in the human.

Atropine.—Kirsner and Palmer (1940) reported that atropine sulfate, given orally in four 1/60-grain (1 mg.) doses daily, did not affect the reaction of the gastric contents though it did apparently reduce the volume of the secretion. They found it very helpful when used as above in addition to alkali therapy, the result in their opinion being due to atropine's prolongation of gastric emptying time as well as its reduction of the volume of gastric secretion. However, Gold (1943) pointed out that such a dose is very high and must cause

considerable discomfort and he questioned that it could really be of any value in view of the notorious resistance of the gastro-intestinal tract to the action of atropine. Despite the fact that most gastro-enterologists say that patients feel better when they are given atropine, I certainly agree with Gold that it would be well to have this matter put to the test by substitution of a placebo with the proper taste or flavor.

Ambulatory with Frequent Feedings (Alvarez Type of Treatment)

While admitting that the Sippy treatment is often effective, Alvarez has the following objections to make: (*a*) it requires more training, enthusiasm and faith in this particular type of treatment than can be expected from the average busy practitioner; (*b*) it requires an expensive month in hospital; (*c*) only a very few patients can be expected to come back to the hospital for subsequent Sippy treatments for each recurrence; (*d*) the lack of evidence that the period of relief after a Sippy cure is longer than after little or no treatment; (*e*) the observation that frequent feeding is perhaps the most valuable item in the cure; (*f*) and the fact that, "whether the profession likes it or not," most patients with ulcer will continue to try to worry through their attacks and keep at their work. In view of these considerations, Alvarez champions a simple form of ambulant-frequent feeding treatment that has the best prospect of being practicable for the average physician and the average patient.

Diet.—The patient is given three good meals daily and the attempt is made to fatten him if, as is usually the case, he is underweight. The only stipulation is that foods which contain scratchy material, such as raw fruit, bran, many of the green vegetables unless puréed, celery, salads, nuts, gristle and berries, are to be excluded (see the "smooth diet" list under Nervous Indigestion). Alvarez is not certain that such care is important, but since many patients experience no great privation with this amount of restriction, he feels that "smooth" dieting should be instituted in most cases. Meat is not forbidden. Windwer and Matzner (1939) in fact proposed that in addition to the use of lean boiled meat, chicken, cottage cheese and milk, the patient take about 8 Gm. of unflavored gelatin in a quarter-glass of water at hourly intervals between feedings for seven doses daily. In justification of this high protein diet these authors alleged the following: (*a*) Proteins can neutralize acids by their acid binding properties. (*b*) Peptic activity may be inhibited by the "competitive retardation" of the products of digestion of proteins. (*c*) The ample supply of amino acids will restore a deficiency believed by some to be a causative factor in the production of ulcer.

The important part of the treatment consists in the taking of food between meals. The mixture used consists of a quart of milk, two eggs and from 1 gill to ½ pint of cream. Of this a glassful is drunk at 10 A.M. and another at 2, 4, 8 and 10 P.M., with an additional one during the night when awake. The patient intolerant of milk may use a thin gruel made from any cereal. In some patients pain will recur within one and one-half hours, in which case the feedings must be taken every hour and fifteen minutes—but Alvarez finds that these individuals usually do not do well on medical treatment. However, Dick and Eisele (1942) described their satisfactory treatment of a series of 41 patients with 1 to 4 ounces (30 to 120 cc.) of a mixture of equal parts of milk and cream at hourly intervals during the day and often during the early evening, using milk alone in a few instances in which cream was poorly tolerated.

Vitamins.—See under Sippy treatment on a preceding page.

Alkalis.—Not routinely used in this type of treatment.

Exercise.—The patient is to rest as much as possible on Saturdays and Sundays. Walking is about the only exercise that is allowable at any time; golf, gardening and any bodily movements that are likely to cause pulling on the duodenum are to be given up. "One must remember that the first portion of the duodenum serves as a sort of hook from which the stomach swings like a hammock, and I believe that this anatomic arrangement has something to do with the tendency toward ulceration at that point. Men often say that it is the hard work in spring or fall, plowing or pitching hay, which brings their recurrences; and I have seen a number of cases in which, even after operation, the patient could stay well only by avoiding lifting and bending. In fact many persons can obtain permanent relief only by changing to a sedentary occupation."

Duration of Treatment.—Most patients are quickly made comfortable on this regimen but they must nevertheless persist in it for six months or preferably a year. Many will remain free from discomfort thereafter only if they abstain from exercise and take small bits of food in the middle of the morning, once or twice in the afternoon, and perhaps again before retiring. Alvarez (1944) has recently reminded us that the patient with ulcer is most in danger of a flare-up or a catastrophe during the hours immediately following a distressing emotional storm, and he therefore suggested that when a patient goes through such a crisis he should not wait for the expected flare-up or hemorrhage or perforation but should immediately start taking food every hour or two; the extra feedings probably most needed are those between the hours of 10 P.M. and 3 A.M.

Aluminum Hydroxide and Aluminum Phosphate

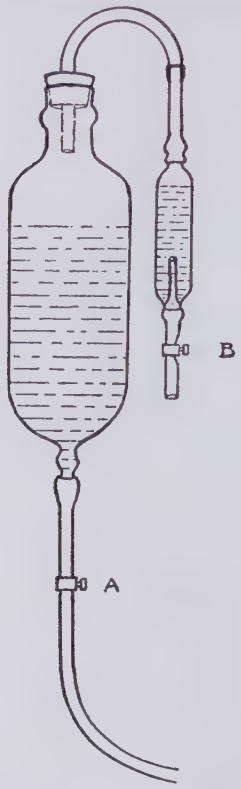
The French custom of using aluminum hydroxide as an antacid devoid of deleterious effects was introduced into America by Crohn, in 1929, but it is the more recent work of Einsel and Woldman and their respective associates that has established it in its present place of high esteem in this country. More recently, because of considerable phosphate losses in the feces of dogs treated experimentally with aluminum hydroxide gels over long periods, many men have substituted basic (hydrated) aluminum phosphate for aluminum hydroxide in this type of treatment.

The method of treating peptic ulcer with aluminum gels resembles the classical Sippy method in that very ill patients are kept in bed on frequent feedings of a bland diet; it resembles the Alvarez method in that less severely ill patients are maintained in an ambulatory state with quite similar frequent feedings. But it differs from these methods of treatment in that it substitutes for the alkalis of the Sippy regimen, and the lack of alkalis of the Alvarez regimen, the frequent administration of these acid-neutralizing colloidal aluminum gels. These substances have a high acid-combining power and a desirable degree of astringency and they coat the ulcer surface with a protective jelly-like mass. Unlike the carbonates, they do not liberate large quantities of carbon dioxide and they are not laxative like the magnesium salts; indeed they are even constipating though the phosphate gel is found the less offender of the two in this regard. Furthermore they do not induce compensatory acid secretion as does sodium bicarbonate; and since they are not absorbed and thus cannot disturb the acid-base balance they do not cause alkalosis. There

are now available many highly favorable reports of this method of treatment, all agreeing that pain is rapidly relieved (usually, indeed, within twenty-four hours), healing rapidly accomplished (*i.e.*, niches frequently disappearing in seven to ten days and larger craters filling in two weeks), results often obtained with this treatment in patients in whom other methods have failed, and an incidence of recurrences certainly no greater than with other methods.

FLASK FOR DRIPPING COLLOIDAL ALUMINUM SUSPENSIONS

(After Woldman and Rowland)



Technic.—1. Fill the Kelly (larger) flask to the top with a 1 per cent suspension of colloidal aluminum hydroxide or phosphate while clamp (*A*) is closed. 2. Fill the inverted Murphy drip tube with water while clamp (*B*) is closed. 3. Insert the rubber stopper securely into the mouth of the Kelly flask and connect the inverted Murphy drip tube to the short rubber tube with screw clip as indicated in the diagram. 4. Attach Kelly flask to a hook or standard 2 to 3 feet above the level of the patient's stomach. 5. Open clamp (*A*) wide. 6. Open clamp (*B*) just enough to allow air to bubble slowly through the water in the Murphy drip tube (about fifteen bubbles a minute). 7. After the rate of flow is established and the nasogastric tube is comfortably in position, attach the outflow tube to the nasogastric tube by a glass connection.

Drip Administration.—This method requires hospitalization but it is the preferred method to accomplish rapid healing and also the necessary method in very ill patients. The colloidal aluminum preparations are continuously instilled into the stomach through a nasogastric tube at the rate of 15 drops per minute, day and night, for ten days in average cases. The earlier troubles from

clogging of an ordinary Levin tube and complaints when a larger Levin tube was used have now been overcome by the substitution of a soft collapsible thin rubber tube about $\frac{1}{4}$ inch in diameter. This tube is passed through the nose into the stomach with the aid of a silkworm-gut suture which acts as obturator and is left in place within the tube to prevent its kinking. The tube is passed only as far as the end of the esophagus. The older three-flask method of delivering the solution has now been replaced by the one-flask method of Woldman and Rowland (1941) depicted and described herewith.

Since the astringent action of aluminum hydroxide tends to cause constipation, mineral oil is usually given daily, or an enema every other day; these laxative measures may be unnecessary if the phosphate is used.

Oral Administration.—When patients object to or cannot tolerate the tube, the drugs may be given by mouth in an average dose of 1 to 2 drachms (4 to 8 Gm.) stirred up in a little water at intervals of one hour during the day and every two hours during the period of sleeping, giving a sedative in the evening so the patient will go quickly back to sleep when roused throughout the night.

Ambulatory Routine.—In the experience of Collins *et al.* (1941), treating 154 patients who carried on in their usual occupations, the following routine was satisfactory, though of course it had to be modified according to severity of symptoms: (*a*) a dose of aluminum hydroxide every two hours during waking hours for the first three months, either a meal or a glassful of milk being taken midway between the doses; (*b*) during the next three months, a glassful of milk midway between meals and a dose of the drug one hour after each meal, after each glassful of milk, and at bedtime; (*c*) during the remainder of the first year's treatment the taking of the drug after the three main meals and at bedtime. A good many men have substituted aluminum phosphate for aluminum hydroxide in this type of treatment because of the alleged disturbance of phosphorus balance when the hydroxide is used; but Freeman (1942), who has actively participated in these phosphorus studies, reviewed all the available data and stated that they do not furnish adequate proof that the ulcer patient who is maintained on a phosphorus-rich diet (*i.e.*, who is obtaining considerable milk and cheese) will experience a phosphorus deficiency as the result of using aluminum hydroxide as an antacid.

Alkalinized Milk Drip

This is the original drip method, introduced by Winkelstein, of the Mount Sinai Hospital in New York, in 1931. The preparation employed consists of milk heated sufficiently to remove the chill and containing 5 Gm. of sodium bicarbonate to the quart. This is allowed to drip into the stomach at the rate of 30 drops per minute. Originally the drip was administered continuously throughout the twenty-four hours for two or three weeks, but Winkelstein *et al.* (1942), reviewing ten years' experience with the method, said that in recent years the treatment had been modified as follows: the patient receives three liberal bland meals daily and atropine with the usual sedatives; one hour after each meal the drip is started and it is continued until one hour before the next meal, even while the patient sleeps at night. More recently, Winkelstein (1944) has said that in mild cases the patients treat themselves only during the night. According to Winkelstein the milk drip is contraindicated in pyloric obstruction and in renal disease because the absorbable alkali may aggravate a systemic alkalosis; it is also contraindicated in patients who manifest allergic reactions to milk or who experience intestinal disturbances

from it. That the milk drip is still preferred under some circumstances to the aluminum drip by some men is indicated in the report of Rush (1943) who has used it in the Army as an adjunct in making the diagnosis of peptic ulcer; he found that patients with ulcer all experienced prompt relief from milk drip therapy but that patients with a functional gastro-intestinal disturbance almost uniformly failed to express more than transient relief of their symptoms upon the employment of this type of treatment.

Miscellaneous Types of Therapy

The following methods of approach no longer seem to me to merit space for their description: physiologic rest through venoclysis (Hendon type of treatment); milkless diet with white of egg and butter (Jarotzky type of treatment); mucin treatment; histidine treatment.

Metz and Lackey (1940) reported good results following the supplementary employment of powdered posterior pituitary preparation as in diabetes insipidus, and in 1943 they brought their series up to 311 cases with a claim of satisfactory results in 74 per cent; their work remains unconfirmed. In 1938, Bergh reported that the oral administration of bile salts was helpful in a large proportion of a small series of cases, but in the same year the independent findings of Emery and Schnitker were not nearly so favorable.

Treatment of Hemorrhage

The indications here are to combat shock, combat dehydration, prevent digestion of the clot and of the edges of the exposed blood vessel, promote clot formation, restore the blood volume and maintain nourishment. In some instances resort to surgery is necessary.

Shock.—Morphine (or dilaudid) is used by most men hypodermically not only because of its influence in quieting the patient physically but because it greatly reduces fear, which is a contributing factor of great importance in shock. However, Nicholson and Miller (1941), and Schiff (1944), have opposed the use of these opiates because of their known tendency to produce nausea and vomiting, symptoms that one is trying to combat. The latter stresses the fact, previously brought out by others, that the relaxation in the tone of the duodenum occurring a few minutes after the administration of morphine might interfere with the constriction of an open vessel in the duodenal wall. Schiff prefers phenobarbital. One might give one of the following hypodermically: pentobarbital sodium, 3 grains (0.2 Gm.); barbital sodium, 5 grains (0.3 Gm.); phenobarbital sodium, 2 grains (0.12 Gm.); amytal sodium, 3 grains (0.2 Gm.); or chloral hydrate, 20 grains (1.2 Gm.) in a little water, may be introduced into the rectum.

Dehydration.—This condition is combated by proctoclysis or hypodermoclysis with saline or Locke's solution, or by the intravenous administration of dextrose. It has not been proved that rectal administration of fluid stimulates gastric motor activity. These fluids only counteract dehydration; *i.e.*, they do not restore blood volume. Some men have used 6 per cent acacia intravenously. Kirsner and Palmer (1939) strongly opposed the intravenous administration of any fluid in cases of massive hemorrhage, noting that in 4 of the 5 fatalities in their series intravenous fluids had been given without showing even temporary evidence of improvement. A frequent practice is to elevate the foot of the bed to "help the cerebral circulation"; Wood (1936) pointed

out that venous return from the head may be so much impeded in this way as to contribute to the stupor by promoting cerebral edema.

Protect the Bleeding Area.—The employment of alkalis to prevent digestion of the clot through acid neutralization has theoretical justification and many men do so use them. However, Schiff (1944) said he was not convinced that alkalis were important in preventing clot digestion and that he used them only in the presence of pain.

A few years ago Soper proposed continuous lavage, establishing siphonage to a bottle and thus keeping the stomach cleaned out; it was his feeling that the raw surface is protected from corroding gastric juice by this method and that nausea and vomiting are prevented and the patient kept remarkably comfortable. On the third to fifth day he passed a tube on down into the intestine and introduced through it a high calorie mixture of raw eggs, milk, cream and lactose. This method provoked adverse criticism when it was introduced, but Soper pointed out that no one criticized who had used the tube; in 1936, he (Thompson and Soper) reiterated his confidence in the method.

Promote Clot Formation.—Quiet, of both body and stomach, is of course the chief measure here. The application of an ice-bag to the epigastrium is thought by many practitioners to be of value; to me it seems that it can be of aid only in helping to hold the patient motionless. Smithies (1935) and Andresen (1939), pertinently pointing out that such a measure only further chills a patient already in shock, preferred the opposite and more rational measure of keeping the patient warm.

None of the alleged hemostatic agents have proved to be of any worth.

Woldman (1941) used his aluminum hydroxide treatment (described earlier in this article) with apparently excellent results in 144 patients: in 86 by the drip method, in 42 by the mouth only and in 16 by a combination of the two methods. He contrasted the mortality rate of 2 per cent in this group with the rate of 28 per cent in the same hospital during the five years preceding inauguration of aluminum hydroxide therapy. It is alleged that this agent promotes clot formation and then protects the delicate fibrin from the action of strong unbuffered gastric juice.

Restore Blood Volume.—It is now almost unanimously agreed that transfusion of blood for the restoration of blood volume is indicated in many cases of hemorrhage. The continuous drip method, introduced by Marriott and Kekwick in 1935, is the one most frequently employed: citrated blood is given at the rate of 3 to 5 ounces (90 to 150 cc.) per hour, which usually raises the hemoglobin 10 per cent if the bleeding has stopped. Wood (1936) said that the hemoglobin may be elevated to 70 per cent in twelve to forty-eight hours with continuous administration of blood. Schiff (1944) listed the following indications for blood transfusion in cases of hematemesis or melena: a pulse rate of 140 or more, hemoglobin of less than 5 grams per 100 cc. (less than 35 per cent), a red count of two million or less, systolic blood pressure of 90 mm. or less, a blood urea nitrogen of 50 mg. per 100 cc. or more or a persistent elevation or rising concentration, delirium or persistent headache, marked restlessness uncontrolled by other means, and general "poor appearance."

There have been some potent opponents of blood transfusion in this type of hemorrhage, most notably perhaps Hurst and Ryle (1937), in England, and Crohn and Lerner (1939) in the United States. The latter felt that transfusions should be used stintingly and in small amounts preferably after the blood pressure has stabilized and when the symptoms of shock have subsided—threat-

ened death due to anoxemia is the only immediate indication which they recognized.

Black and Smith (1941) found that plasma transfusions affected their patients adversely.

Maintenance of Nourishment.—In the main, the surgeon and the internist have taken positions in opposing camps on this subject.

Starvation.—Many surgeons still favor the keeping of all food out of the stomach for several days, employing dextrose intravenously either intermittently or by venoclysis, or feeding by rectum. It must be admitted that not much nutriment can be introduced by the latter route, since we are limited to the giving of dextrose, peptones and alcohol. The following is a typical formula, the whole of this mixture being introduced into the rectum by the drip method three or more times in twenty-four hours.

℞	Witte's peptone	℥j	30.0
	Alcohol	℥ss	15.0
	Glucose syrup	℥j	30.0
	Saline solution to make	℥viij	250.0

I have not seen any report as yet of the parenteral administration of amino acids in peptic ulcers.

When mouth feeding is resumed (generally about two days after a rising blood pressure, slowing pulse with improved quality and an improving blood picture indicate cessation of bleeding), it is usual to begin with frequent feedings of barley gruel and fruit juices, adding custards, strained soups and puréed vegetables gradually, and allowing meats which tend to increase acid secretion only much later.

Generous Feeding.—Most internists have now embraced the viewpoint that an empty stomach is never at rest and that it should be kept at least partially filled from the beginning with food that combines readily with gastric juice and does not overstimulate its production. At the Long Island College Hospital, where Andresen introduced a liberal feeding method in 1916, the following liquid mixture is used: gelatin, 30 Gm.; dextrose, 60 Gm.; cream (20 per cent), 100 cc.; milk, 900 cc.; the formula to be made fresh every twelve hours and kept cool but not placed in the refrigerator in order to avoid jelling. For the first four days, the patient receives 6 ounces of this mixture (chocolate, vanilla, coffee, or tea flavored if desired) every two hours. On the fifth and sixth days any one of the following is added to 4 of the feedings:

1 egg—soft boiled, poached, or raw
Cereal—3 ounces
Custard, jello, or ice cream

On the seventh and eighth days, two of the above foods are added to each of 3 feedings, and on the ninth day the patient goes back on to regular ulcer diet. If at the beginning of the above-outlined regimen the patient cannot tolerate the thick gelatin-milk mixture, he is given for a while the following formula: gelatin, 30 Gm.; dextrose, 90 Gm.; juice of 2 oranges; water, 1000 cc.

The similar full-feeding regimen of Meulengracht in Denmark, adopted apparently some time after Andresen's first publication, has caught the medical fancy more fully here in America, probably because it was originated further away. Schiff (1944), who studied the matter in Meulengracht's clinic in Copenhagen, has adapted the diet to American conditions; he employs milk, cream, butter, eggs, strained cereals, puddings, puréed vegetables and

fruits, ground, scraped, or minced meat, white bread, plain or toasted, and additional beverages such as weak tea or cocoa. The diet contains about 2500 calories and 50 mg. of vitamin C and is adequate in mineral and salt content. Feedings are given at two-hour intervals beginning at 8 A.M. and ending at 8 P.M. Between feedings the patient is allowed water or milk in quantities up to 5 ounces as desired. Schiff's modification of the Meulengracht diet is presented in Table 21.

There are many reports of the satisfactory employment of the full feeding regimen in bleeding in ulcers but of course it does not succeed in every case. In their appraisal of various methods of treatment, Rafsky and Weingarten (1942) were able to follow the regimen without interruption in 26 of the 39 patients in whom it was tried; discontinuance was due to the following factors: recurrence of bleeding in 7 patients, 3 of whom died; severe pain in 3, 1 of whom had a perforation of his ulcer and died postoperatively; and severe nausea and vomiting in 3. Wheeler (1943) has pointed out that the principal advantages of full feeding are that the patient seems to get more prompt relief of pain, the bleeding apparently stops just as quickly, and the stay in hos-

TABLE 21.—MODIFIED MEULENGRACHT DIET (SCHIFF, 1944)

Time of Feeding	Food	Wt. in Gm.
	First and Second Day	
8 A.M. Breakfast	Orange juice	30
	Toast	20
	Butter	10
	Milk	75
	Cream	75
12 M. Dinner	Vegetable purée	60
	Pudding	100
	Cream	30
	Orange juice	30
4 P.M.	Milk	75
	Cream	75
	Fruit purée	60
	Pudding	100
	Cream	30
6 P.M. Supper	Bread	20
	Butter	10
	Fruit purée	60
	Pudding	100
	Cream	30
	Milk	75
	Cream	75
10 A.M.	Eggnog	
2 P.M.	Milk	150
8 P.M.	Egg (1)	50
	Sugar	5
	Soda cracker (1)	
	Butter	5

Milk and water in volumes up to 5 oz. are allowed between feedings as frequently as patient desires.

TABLE 21.—*Continued*

	Third day on	
8 A.M. Breakfast	Orange juice	30
	Strained cereal	90
	Cream	60
	Toast	20
	Butter	10
12 M. Dinner	Minced meat	60
	Mashed potato	100
	Vegetable purée	60
	Toast	20
	Butter	10
	Fruit purée	60
	Milk	90
	Cream	90
	Orange juice	30
4 P.M.	Milk	180
	Chocolate paste	20
6 P.M. Supper	Cottage cheese or minced meat	60
	Bread	20
	Butter	10
	Pudding	100
	Cream	30
	Milk	90
	Cream	90
	Orange juice	30
10 A.M.	Eggnog	
	Egg (1)	50
	Milk	150
	Sugar	5
	Soda cracker (1)	
	Butter	5
2 P.M. 8 P.M.	Eggnog	
	Egg (1)	50
	Milk	150
	Sugar	5

pital and the time required to bring the blood count back within normal limits appear to be greatly shortened. He points out however that before starting to treat a patient with a bleeding ulcer one should feel sure that it is not perforated or is not about to perforate; in addition to patients whose board-like rigidity of the abdomen presents frank evidence of perforation, he recognizes the following criteria for impending perforation—a history of unusually severe and persistent pain, particularly marked tenderness on abdominal palpation, undue fever or leukocytosis, or the finding of penetration in recent roentgenologic studies of the gastro-intestinal tract.

Resort to Surgery.—Surgical statistics are not in complete agreement regarding indications for intervention, which likely means that medical and surgical judgment must still weigh each case separately. However, I believe that all observers, even those surgeons who hold that Finsterer's "first forty-eight hours" is still the optimum period for surgical attack in the bleeding of chronic peptic ulcer, will agree that young individuals with bleeding ulcers

rarely die and that when they do it is usually as a result of complications rather than exsanguination. Blackford and Allen (1942), in the conclusion to their statistical study of the 151 fatalities from hemorrhage in peptic ulcer recorded in Seattle, Washington, during the period 1935 to 1941, found evidence nevertheless that many patients past forty-five have repeated hemorrhages from peptic ulcer and continue to live on medical treatment for many years. They felt that the lives of some medically treated patients might have been saved had operation been performed but that it is equally true to say that as many patients might have died following surgery. Hinton's (1942) long experience in an ulcer service at Bellevue Hospital in New York City has taught him that the transfusion test will decide the indications for surgical intervention in massive hemorrhage: transfusions in amounts of 1000 to 5000 cc. of blood are given by the indirect method and if the pulse and blood pressure have not improved or if they have become worse it is considered a fair indication that there is arterial bleeding which will prove fatal. It seems to me that Martin (1943) made a very important point in stressing the fact that patients who are seen on a surgical service are much more likely to be in a most serious condition because they have either been transferred from a medical service where they have bled severely or long or they have been admitted from the accident ward where the bleeding is usually dramatic, either as to the speed or the total amount; one can expect the mortality from hemorrhage among ambulatory patients or patients retained on the medical wards to be much lower.

Treatment of Acute Perforation

Acute perforation demands immediate surgical intervention. Most patients recover who are operated upon within six hours after the perforation has occurred; for each hour after that time the chances of death are greatly increased. In a review of 100 cases in which operation had been performed for perforated peptic ulcer, the average length of the follow-up period being three years and four months, Williams (1944) found that results had been excellent in 28 per cent, good in 27 per cent, fair in 22 per cent and poor in 23 per cent of the cases.

COLON CONSCIOUSNESS

(*Constipation, Mucous Colitis, Unstable Colon, Spastic Irritable Colon, Visceroptosis*)

This condition can no longer be satisfactorily presented as comprising several distinct entities each resting upon its separate pathologic basis, for the unity of the functional disorder underlying them all has now been firmly established. It is primarily a disturbance of the conditioned reflex upon which normal defecation depends, characterized by changes in colonic tone, irritability and secretory activity, induced by environmental imbalance in a neuropathic individual, aggravated by "treatment," and expressed as awareness of the colon and its activities. The normal physiologic behavior of the colon and rectum is quite simple. When a meal is taken the ileocecal valve is relaxed and the contents of the ileum are propelled by peristaltic action into the cecum and ascending colon. Simultaneously, waves of contraction sweep along the colon to convey the contents into the pelvic portion, haustrations (seg-

mental movements) at the same time serving to effect intimate contact with large surfaces of the mucosa so that water is absorbed and the feces converted into their final form. In the infant there is no mental control of the terminal stage of this stuffing process, a lack with results that are well known. But in the course of time—I am following Hurst closely at this point—an elaborate conditioned reflex develops, in which getting up in the morning, a bath, dressing, breakfast and finally sitting down in the familiar w. c. take part, with the result that the biggest colonic peristaltic wave of the twenty-four hours takes place, the rectum is filled, there is the "call to defecate," the diaphragm and abdominal wall are voluntarily contracted, and contraction of the rectum with relaxation of the anal sphincter permits the feces to be evacuated. In most adults this scene is enacted diurnally, but not in all, for there are many individuals who skip one or several days and are not in the least disturbed provided their absorption with life is properly extroverted. The colon-conscious fellow is troubled, though! For not only does he come complaining of the number of days he has failed to have an evacuation, but he knows that the stools, when they do oblige him, are ribbon-like, pencil-shaped, accompanied by much mucus, and so on; and he clamors for the opportunity to tell about these things to assist the doctor, whose mind's eye is of course ever steadily fixed on the standard stool encased with the meter bar in Paris. More often than not he is also wedded to the fascinating idea of "autointoxication," about which faddists (not all outside the profession) and the daily newspapers hold forth with unremitting gusto; so that many times the stool he tells about is really only dimly remembered, since for months or years he has kept himself satisfyingly mushy, or even in a state of chronic diarrhea, with drugs. Or the bowel is washed out with enemas or irrigations, at home or in commercial establishments which exist for the purpose. The abdomen is of course often tender in colon-conscious patients and the descending colon may be palpable as a tender cordlike structure; sometimes there are paroxysms of severe abdominal colic. "Visceroptosis" is a term which has caught on well with these patients, though scientific proof is still lacking that a cecum offends heinously by mere residence in the pelvis. Not all of those who know of their affliction escape the surgeons, and those who do are almost certain to control themselves by day with monstrous binders and by night with prodigious exercises in the bed, the latter usually culminating, I believe, with a slide down onto the abdomen from the knee-chest position so that everything will remain safely tucked up during the long dangerous night.

THERAPY

In an ancient recipe for rabbit stew one is enjoined to "first catch your rabbit." How sound that advice is when applied to the subject in hand; first be sure that the patient before you is suffering from simple colon consciousness before you undertake to treat him. Gynecologic, proctoscopic, sigmoidoscopic, roentgenologic, internologic (if I may coin the word) examinations may reveal many primary or secondary organic causes for the syndrome: adhesions, pressure of other organs or of new growths upon the bowel; reflexes from eyestrain; early pulmonary tuberculosis or thyrotoxicosis; chronic appendicitis; gallbladder disease; inflammation of the female adnexa, or of the stomach, liver or pancreas; and so on. There are many resemblances between allergic states and the condition of being colon conscious, especially in those instances in which the symptoms are of intermittent and spasmodic nature. Should it be

possible to determine the offending substance and to eliminate it from the diet, or environment, or even to desensitize the patient to it, much misery will be avoided and a near-miracle performed. The matter does not find such simple allergic solution nearly so often as could be desired; still, any case may always be the lucky one. In summary, then, the patient must be given the benefit of thorough examinations of all sorts, and only if these are convincingly negative is he to be assigned to the group under present consideration.

Psychotherapy.—Read the brief presentation of Alvarez' psychotherapeutic approach to the patient with nervous indigestion (see Index). Indeed, there seems to be little difference between patients suffering from one or more forms of "indigestion" and those bothered by awareness of the colon and its performances, save that the latter center their disturbances lower in the tract. All of these individuals need readjustment to something in themselves or in their environment. It is the practitioner's duty to find that something, then to lead the patient to face and live with it. I know nothing easier to set down in a few words!

Habit and Defecation Posture.—The stool should be visited by every person every morning after breakfast. Too often housewives who are busy at this time, and men who take their breakfast at a quick-lunch counter en route to the office, "put it off" until the desire is no longer felt. After the conditioned reflex has become dulled through such disregard and "constipation" has set in, if one impresses the necessity of the regular daily visit upon these people they often accept the advice and carry it out with a grim determination which easily defeats their purpose, for defecation is accomplished only by the maintenance of a nice balance between contraction *and* relaxation. A few puffs of a cigaret, a few peeps at a newspaper or magazine, is a recipe well known to many persons. Sometimes placing the feet upon the round of a chair so that the thighs are flexed on the abdomen is helpful; the principle is anatomically, physiologically and traditionally sound—surely the early morning sun the world around still catches the majority of mankind squatting upon its heels at this daily duty. In infants one must also reckon at times with lack of ability or desire to use the expulsive forces necessary for defecation.

Exercise.—Bodily exercise is of value in the promotion of general well-being, and if it can be taken in the form of some competitive game in which the maladjusted hypochondriacal patient will lose himself for awhile, may be counted upon to be of considerable assistance in the treatment of these cases. But in and of itself it probably has little value; even letter carriers, who could never be rightly accused of a sedentary existence, are said to be a constipated lot. Massage of the abdominal muscles, or rolling a heavy ball about over the abdomen, is nowadays frowned upon because of the danger of doing injury to deep structures by abuse of these measures.

Water Drinking.—Some years ago Bastedo (1936) had a number of patients drink one glass of water every hour for fifteen hours daily for one week. The regimen caused diuresis but it did not increase bowel movements, and this is what might be expected since water is absorbed principally in the right half of the colon and the dry hard stool which disturbs the patient with colon consciousness is much further down than that. However, many physicians recommend that their constipated patients take large quantities of water every day; a few years ago Adson and Bargen (1936) were recommending between $2\frac{1}{2}$ and 3 quarts (2.5 and 3 liters). Some patients like to add ordinary table salt to some of this water and others put in some sauerkraut juice.

Persons who treat themselves in this way must have happy lives shuttling between the water cooler and the conveniences.

Diet, Bran, Agar, Psyllium, Metamucil, Karaya Gum and Beet Pulp.—Present belief is that the colon of the patient suffering from functional disturbance of the organ is practically always in a spastic state due to hyperirritability, and that the best thing to do for such a colon is to give it rest by the use of a smooth diet (see Nervous Indigestion). The rational thing is to take the patient off his beloved cathartics and enemas and wait to see what happens after a while on a smooth diet; in some instances it will be necessary to use more raw fruits and green vegetables than that diet provides, in others not, but there is no way to predict this until the colon has been allowed to fill after the punishment ceases. The old division of constipation into two types, spastic and atonic, has fallen down under more careful study, and with it has gone the conception that the chief trouble in the atonic variety was that the patient ate too little roughage and therefore needed to gorge himself on such things as lettuce, celery, endive, spinach, carrots, beets, string beans, figs, dates, raisins and prunes. It is true, as already said above, that some individuals seem to need more bulk in the bowel than others, and the above foods provide this nicely, but such individuals are certainly in the minority and there is now believed to be little justification for excessive roughage feeding of every person in whom roentgen study after a barium meal or enema shows evidences of decreased colonic tone. An occasional patient will get a nice effect from a small amount of bran in the form of cookies, muffins, bread, cakes, or taken with sugar and cream to replace the morning cereal, but leading gastro-enterologists are now firmly opposed to its use in most cases since it robs any diet of whatever property of "smoothness" it may have had. Certainly all individuals should be warned against using bran on the principle that if a little is good a lot is better; it is not surprising that there are on record one or two instances in which silly individuals have actually stuffed the gut with this dry material until they produced obstruction. Olmsted *et al.* (1936) used 1 to 2 tablespoonfuls of beet pulp with satisfaction in a small series of cases. Some observers have found that bulk can be satisfactorily provided without irritation through the use of 1 or 2 tablespoonfuls of ordinary x-ray barium taken in water two or three times daily. Some colon-conscious patients are made worse not only by the physical irritation of roughages but also by the fact that they suffer from excessive intestinal fermentation (see Index) and they therefore react to these cellulose materials by the production of large amounts of gas. Agar passes through the intestinal tract without undergoing bacterial digestion and merely softens and adds bulk to the feces by virtue of its property of retaining water. It is best used in the form of shreds or a coarse powder, for when finely pulverized it too may produce colic, according to Fantus. It is usually employed in several tablespoonful doses incorporated with foods at the table, though currently during War II it is not easily obtainable. Psyllium is a small brown seed that exudes a considerable amount of mucilaginous material when it is moistened. The dose is 2 to 4 teaspoonfuls stirred up with twice as much hot or cold water until a gelatinous mass is formed, which is then spread on bread or taken with cream and sugar, with stewed fruit, or in soup; some people like to place the seed in fruit juice and drink the mixture with mastication. A mixture of psyllium and agar is commercially available as is also the preparation known as metamucil, a 50 per cent mixture of dextrose and an extract from the psyllium seed; a rounded teaspoonful of metamucil is stirred into a

glass of water, milk, or fruit juice three times a day and followed with a large glass of water. Thienes and Hall (1941) found that psyllium caused pigmentation of the kidneys in experimental animals, but that neither in these animals nor in 9 patients who were long-time users of the agent did it cause any evidences of damage to renal function. Karaya gum, which absorbs and holds a large quantity of water in the tract, is the newest of the agents of this type which exert their effect by physical rather than chemical action; it seems to cause intestinal irritation in some instances and Alvarez (1940) reported a case in which migrainous attacks were attributable to the use of this agent; karaya gum comes from India and has not been easily obtainable during War II.

The Enema.—Ordinarily one of the chief indications is to break a vicious enema habit, which can best be accomplished by sharply forbidding further resort to the measure; still, this is an ideal which, as in all the affairs of man, can often only be approximately realized or must at least be approached through a series of compromises. When it is felt than an occasional enema must be allowed during the time that one is waiting for sound psychotherapy plus cessation of routine dosing, to bring about normal evacuation, it is well to bear in mind that a pint of cool water containing a teaspoonful of sodium chloride or sodium bicarbonate is to be preferred to the ordinary soap-suds enema, which is so irritating to even the normal bowel that for some time after its use the mucous membrane presents an angry red appearance. Perhaps it is more rational to inject a small amount of oil at night as a retention enema; about 3 ounces (90 cc.) of cotton seed oil or liquid petrolatum, warmed; olive oil is likely to be irritating. The older custom of injecting large quantities of oil upon retiring, and to make an elaborate ritual of the procedure, is no longer in favor. If the feces have already become impacted, the reader should bear in mind that the injection of water, not oil, is indicated. When use of an irritant is actually required, Levy has employed a mixture of 5 cc. of rectified oil of turpentine, 25 cc. of cotton seed oil, 45 cc. of glycerin and 45 cc. of soft soap. One to 2 teaspoonfuls of this mixture are added to 4 ounces (120 cc.) of water and injected into the rectum by means of a rubber bulb syringe. The action is quick and complete only because this concoction is violently irritating.

Suppositories.—Graham pointed out some years ago that if rapid evacuation of the rectum and colon is desired, a 5-grain (0.3 Gm.) quinine dihydrochloride suppository will promptly produce a large but not watery stool. Glycerin suppositories have of course been in use since time out of mind.

Colonic Irrigation.—Bastedo is perhaps the principal champion in this country of the use of colon irrigations in so-called "mucous colitis"; Friedenwald and Morrison, and a few others, favor the method also. But the vast majority of those who confine their practice largely to gastro-enterology flay the procedure as being based upon an entirely erroneous conception of the nature of mucus secretion in the bowel. Hurst pointed out that the mucous membrane of the colon, like all other mucosae, secretes mucus as a response to both mechanical and chemical irritation as a sign of healthy activity. The passage of dry hard feces is often thus facilitated. When a purgative is taken, the irritation likewise induces considerable secretion, and rapid passage permits much mucus to appear in the loose stool. An enema, especially one containing an irritant, will do the same thing. It is true that the long colonic irrigation will oftentimes bring away masses of mucus, but I think that one of Hurst's case reports, with his comments thereon, offers an illuminating explanation for the phenomenon. "A boy of 18 has always had a tendency to con-

stipation and had been continually dosed by his mother with aperients. His report stated that he had been given an irrigation of 30 pints, the treatment lasting one hour and ten minutes. 'The first 12 pints brought away loose faeces but no mucus, but after that a large quantity of jelly mucus was passed continously until the end of the treatment.' That is to say, 12 pints of fluid were required to irritate the healthy mucous membrane of this boy sufficiently to produce excess of mucus, but when once it began to be secreted it naturally continued, and there would still have been mucus present if he had received 100 instead of 30 pints.

"The patient is often told that the mucus has been accumulating in his colon for weeks or months and that is why he has never seen it in his stools, whereas the truth is that his mucous membrane is none the worse for a few pints of water, but after the first few pints it has to protect itself by secreting mucus. It is sometimes reported that by the end of the patient's 'cure' little or no mucus is present, the explanation being that the patient's mucous membrane responds at first by the secretion of mucus to the unaccustomed irritation, but after some weeks the mucus-secreting cells become exhausted and go on strike." Soper has maintained that if irrigation is continued long enough, the "foul-smelling material" described by Bastedo can be secured in persons having a normal colon, being in his opinion the normal contents of the ileum changed by the treatment. Krusen reviewed this subject for the Council on Physical Therapy of the American Medical Association, in 1936; it is difficult to find anything very commendatory in his report.

Bastedo's Technic.—The irrigation is given from a height of 2 feet, using either a No. 34 French tube, velvet-eyed with a closed end, inserted about 6 inches, and used for both inflow and outflow of the fluid after the colon has been filled to capacity, or employing the two-tube method in which a 20 to 24 French soft rubber velvet-eyed catheter is inserted 6 inches for inflow, and a 30 or 32 French velvet-eyed closed-end rectal tube (or stomach tube) inserted 3 or 4 inches for outflow. The tubes are inserted about fifteen minutes after an evacuation enema of plain water has cleared the rectum and lessened the chances of disturbances from defecation reflexes. Plain water, slightly above body temperature, is used, usually 6 to 10 gallons in the course of an hour, the first gallon with the patient on the left side with knees drawn up in order to clean out the lower colon, then for the remainder of the time on the back in order for the fluid to reach the cecum. Saline would make the patient very thirsty, and it is doubtful if the vaunted ability of sodium bicarbonate to dissolve mucus outweighs the disadvantages of its stimulation of the kidneys, disturbance of acid-base balance and tendency to cause gas and colic. These irrigations are usually employed every day or two for a week, then every three or four days for several weeks longer, and then once a week for as long as considered necessary.

Cathartics.—The following drugs are discussed because I have not as yet the courage to omit them, but I sincerely hope that the reader is convinced from the matter presented in the immediately preceding pages that until he weans his patient away from their use he will not relieve the syndrome of colon consciousness.

Cascara Sagrada.—This drug is a mild yet reliable cathartic, though one occasionally finds a patient in whom it fails to act. When there is complaint of griping, investigation usually discloses that it is being taken in overdose. The ideal dose is one that will produce a single formed, but slightly soft, stool

in the morning when it has been taken on retiring the previous night. The dose of the aromatic fluidextract necessary to accomplish this is from 1 to 3 drachms (4–12 cc.), taken before meals and at bedtime, or all in one dose at bedtime. The following prescription in which there are 20 minims (1.2 cc.) of the aromatic fluidextract to the teaspoonful, offers cascara in a pleasant vehicle; the tincture of nux vomica, so often given with cascara, is omitted here because I believe its inclusion to be irrational and dangerous from the standpoint of the poisoning of young children getting hold of such bottles.

℞	Aromatic fluidextract cascara sagrada	℥x	40.0
	Syrup cinnamon	℥x	40.0
	Water to make	℥iv	120.0
	Label: 1 teaspoonful one-half hour before meals and upon retiring.		

This dose may be doubled or trebled if necessary, but it should be borne in mind that with cascara it is sometimes possible after a while to reduce the dosage gradually without losing effect. Fantus offered the following dosage of the aromatic fluidextract for children:

	Cc.
Child, 6 months old	1
Child, 18 months old	From 2 to 3
Child, 3 years old	4
Child, 5 years old	From 4 to 8

The adult dose of the plain fluidextract is 15 to 60 minims (1–4 cc.), but this preparation is so bitter that it seems needlessly cruel to prescribe it for adults, and children can hardly be made to take it at all.

Senna.—This drug is more powerful than cascara sagrada and also much more prone to cause griping and general abdominal soreness; it is definitely contraindicated if there is intestinal inflammation of any sort. The dose of the fluidextract is ½ to 1 drachm (2–4 cc.), if taken at one time, or 8 to 16 minims (0.5 to 1 cc.), several times daily. Four to 8 minims (0.25–0.5 cc.) of the tincture of belladonna added to each dose will antagonize griping. The U.S.P. syrup has a full dose of 2 drachms (8 cc.). Such nostrums as "castoria" and "syrup of figs," which owe their chief value to senna, should not be used. Senna may also be pleasantly taken as the U.S.P. compound glycyrrhiza ("licorice") powder; adult dose, 1 drachm (4 cc.) or more, stirred up in water.

Dosage of compound powder of glycyrrhiza for children (Fantus)

Age of child.	Gm.
6 months	0.60
1 year	0.90
2 years	1.20
3 years	2.00
5 years	3.00

Aloe.—The griping tendency of aloe is notorious. The U.S.P. pill contains 2 grains (0.13 Gm.) and the official dose is 2 pills, which is likely to be too large. Fantus offered the following prescription:

℞	Powdered aloe	gr. xxiij	1.5
	Powdered soap	gr. xxiij	1.5
	Mix. Make a mass and divide into 30 capsules.		
	Label: 1 three times a day after meals.		

The active principle, aloin, should be reserved for use only when excessive action is needed; it may be given in a capsule containing ¼ grain (0.015 Gm.).

Phenolphthalein.—This is a yellowish-white, odorless and practically tasteless powder, which has one great fault, namely, that a small dose sometimes acts excessively while a large dose may at times fail to act altogether. Upon the whole, however, the drug is very reliable. It is usually given at bedtime and in the morning produces a stool very much like the normal. The adult dose is from 1 to 3 grains (0.06–0.2 Gm.); infants of eighteen months may be given as much as ½ grain (0.03 Gm.). The National Formulary contains a cocoa and sugar flavored tablet containing 1 grain (tablets of phenolphthalein, N. F.). A great many nostrums rely upon phenolphthalein for their principal or sole active cathartic ingredient; they are for the most part pleasing preparations, but there is no good reason why the physician should not prescribe the drug in its Formulary preparation. A sufficient number of skin eruptions have been shown to be due to the use of phenolphthalein to warrant one in taking this possibility into account in urticarias and erythemas; general constitutional effects, in which circulatory, renal, or nervous disturbances predominate, are much less often reported. Abramowitz thoroughly reviewed the work of himself and others on the subject, in 1935, and his paper, as well as the discussion which followed its reading, leaves little doubt that the reactions are allergic in nature. However, the ordinary acute toxicity of phenolphthalein seems to be extremely low. Blatt *et al.* (1943) reported four cases in children from two to three and one-half years of age who had ingested up to 15 grains (1.0 Gm.) without manifestation of either immediate or delayed toxic reaction. Fantus and Dyniewicz, and Steigmann *et al.* of the same group, in studies between 1936 and 1938, showed that phenolphthalein is not excreted in the milk of nursing women, apparently does not disturb liver function, and would seem to require bile for its activity since it does not induce catharsis in individuals with obstructive jaundice and completely acholic stools. It has been said that the prolonged use of phenolphthalein will sometimes aggravate a preexisting colitis and according to some authorities will even give rise to the condition in a previously normal bowel, though I wonder how accurate the latter statement is.

Salines.—*Magnesium sulfate* (*Epsom salt*): very effective but objectionable in taste; Bethea (1936) said this may be largely overcome by dissolving the salt in one of the palatable fruit juices. A dose of ½ to 1 ounce (15–30 Gm.) is quite large enough. *Magnesium citrate:* principally used as the solution of magnesium citrate which is available as an effervescing preparation in 12-ounce (360 cc.) bottles; dose, 1 bottle or less; nauseating to many people and often quite violent in action. *Milk of magnesia:* palatable and easy to give to children; also an antacid; laxative dose 2 to 4 drachms (8–16 cc.) taken from the spoon or stirred in cold water; addition of fruit juice converts it in part into magnesium citrate which is more active (see above). *Sodium sulfate* (*Glauber's salt*): dose ½ ounce (15 Gm.); extremely nasty. *Effervescent sodium phosphate:* mild but fairly pleasant; dose, 2 to 3 drachms (8–12 Gm.) in water. *Compound effervescing powder* (*Seidlitz powder*): dose, the contents of one blue paper (sodium bicarbonate and Rochelle [potassium and sodium tartrate] salt) and of one white paper (tartaric acid), dissolved separately in water and then mixed; fairly pleasant in taste. *Sodium chloride:* many individuals take about ⅓ teaspoonful of common salt in a glassful of hot water on arising and repeat the dose once or twice while making the toilet, getting a good cathartic effect; this is supposed to be very clever and to teach us doctors something, I have been informed.

Liquid Petrolatum.—Liquid petrolatum is bland, odorless, tasteless, and colorless, and can be taken from the spoon by most patients without any difficulty. It can be easily flavored however. Hinton found that in 500 cc. of the oil any one of the following flavoring oils is satisfactory: anethol, 10 drops; oil of almond, 15 drops; oil of cloves, 10 drops; oil of cinnamon, 5 drops; oil of peppermint, 15 drops; oil of spearmint, 15 drops; and methyl salicylate, 25 drops. Fantus suggested that the oil combination used in the flavoring of aromatic elixir might be used to make liquid petrolatum aromatic; a combination of this sort would be; oil of orange, 2 cc.; oil of lemon, 0.5 cc.; oil of coriander, 0.2 cc.; oil of anise, 0.05 cc.; and liquid petrolatum, 1000 cc.

Emulsification lessens the oiliness of the substance and is said to combat the tendency to leakage. A number of proprietary brands of emulsified liquid petrolatum are now on the market and are well known to all. Of this class of preparations, Fantus wrote: "The worst that can be said about them is that they are more expensive than the same quantity of liquid petrolatum, containing as they do from 25 to 60 per cent of the active agent. The dose of 1 tablespoonful is recommended for them with the suggestion that the activity of the emulsified oil is greater than that of the plain oil, a statement that remains to be proved."

Morgan, in a paper read in the Section on Gastro-Enterology and Proctology at the 1941 meeting of the American Medical Association, severely castigated liquid petrolatum as a cathartic. His charges were that: (*a*) it keeps the rectum partially full most of the time, causing its conversion into an abnormal receptacle for fecal material; (*b*) complete evacuation of the rectum is impossible for there always remains a tenacious layer of a dirty mixture of oil and feces covering the rectal mucosa; (*c*) absorption of carotene, and to a lesser extent of vitamins A and D, is seriously interfered with; (*d*) digestion is incomplete because the passage of the contents through the bowel is hastened; (*e*) the healing of postoperative wounds in the anorectal region is delayed; (*f*) leakage from the anus may give rise to pruritus ani; (*g*) liquid petrolatum may be absorbed and cause pathologic changes in the abdominal viscera. It will be very interesting to see how well this thoroughgoing indictment will be upheld with the passage of time.

Yeast.—Let us leave yeast to the quacks; certainly it is much less harmful than many another substance with which they dabble to the detriment of mankind.

Bacillus Acidophilus.—Since the pioneer writings of Metchnikoff on the dietotherapeutic role of lactic-acid-producing microorganisms, so many hastily set up claims have had to be abandoned, that I think the present attitude of skepticism which most scientists maintain toward the whole subject is not at all to be wondered at. However, we know now beyond doubt that *B. bulgaricus* cannot be implanted in the human intestinal tract and that it is even doubtful whether permanent implantation of *B. acidophilus* ever takes place. A number of very sincere workers have claimed that intractable cases of constipation, or diarrhea, or intestinal fermentation can be controlled or cured by the transformation of the intestinal flora from one that is predominantly gram-negative to one that is predominantly gram-positive—a number of other workers deny this, or at least have failed to succeed with the method. Kopeloff, who has been an indefatigable student of the subject, has found no correlation to exist between constipation and the absence of *B. acidophilus* in fecal specimens; about 50 per cent of individuals seem to harbor the organism. The aim

of this type of therapy is, therefore, to implant the organism by feeding living cultures, and at the same time to give large quantities of lactose to provide the preferred source of energy for the bacterium in the intestinal tract. The amount of lactose necessary seems to be at least 1 to 3 ounces (30–90 Gm.), though much larger quantities are sometimes employed; the required amount of the culture is extremely variable. Weinstein *et al.* (1933) found that when successfully implanted the organism often persists for several weeks after the use of milk has been discontinued; they therefore favor long-continued treatment with periodic interruptions. The monograph of Rettger (1935) and his associates, presenting the results of their many years of study, did not seem to me destined to win many advocates to this type of therapy. Most students feel that implantation can be brought about, if at all, only by the use of the milk preparations and not with such preparations as broth cultures, concentrated cultures, blocks, candies, tablets, or oil suspensions. The milk preparations are marketed in bottles, and should be kept on ice and consumed within the period of time stated on the label, the daily dose being the amount required to accomplish the desired purpose; 500 to 1000 cc. is probably the average daily adult dosage. No *B. acidophilus* preparations are described in New and Nonofficial Remedies (1944).

Treatment of Colic.—Morphine or dilaudid is of course contraindicated here because of the frequent recurrence of the attacks; it should be remembered that the new drug, demerol, is also addictive. Bastedo finds that castor oil by mouth and a hypodermic of codeine phosphate, ½ grain (0.03 Gm.), and atropine sulfate, 1/65 grain (0.001 Gm.), plus hot applications to the abdomen in the form of a hot water bag, electric pad, poultice or stupe (for method see Pneumonia), or a hot bath, will be followed by relief and sleep in most instances. If this fails, however, he irrigates, and if relief is still not obtained, puts the patient in the knee-chest position and slowly injects into the colon ½ to 1 pint (250–500 cc.) of warm olive or cotton seed oil, the injection often being followed after a few hours by the passage of an abundance of mucus and the disappearance of the colic.

In some cases of colon consciousness there may be more or less constant pain though true attacks of colic do not appear; atropine sulfate, or the extract or tincture of belladonna in comparable dosage, is used by many men in such instances, giving the drug three or four times daily for five or six days and then allowing the same number of days to elapse without it.

NONSPECIFIC ULCERATIVE COLITIS

Ulcerative colitis is characterized by inflammation of the mucous membrane and walls of the large intestine, in the pathologic picture of which ulceration predominates. This ulceration usually begins in the rectum and spreads upward eventually to involve the entire colon. It may, however, affect any one part, or several separated parts, of the tube. The course is in most cases a chronic one, extending over months and years, but the symptoms are not usually continuous during this time for there are often long periods of remission between severe attacks of the malady. The symptoms are fever, malaise, prostration, protracted and persistent diarrhea with some tenesmus, and the pas-

sage of blood, mucus and pus. Distress from gas, and griping and other sensations along the course of the colon, are often experienced. Much weight is lost, a peculiar gray pallor is common, and varying degrees of anemia exist. In very severe cases, the body has a peculiar odor and the face a hopeless expression. Bargen has described a diplostreptococcus as the causative agent in many cases of the disease, but there are few who agree with him; the very thorough study of the fecal flora in ten cases, performed by Rodaniche, Palmer and Kirsner (1943), revealed *Streptococcus fecalis* as the predominating streptococcal species in the feces and the only streptococcus found constantly in all the cases. Dack considered *B. necrophorum* the probable offender. Buttiaux and Sévin thought that certain organisms ordinarily regarded as saprophytic, such as *Escherichia coli*, might under some circumstances have their virulence enhanced, but Nicoll's later study indicated that the assumption is probably gratuitous with regard to *E. coli* at least. *Endamoeba histolytica* and *Balantidium coli* have not been overlooked, but most observers feel it entirely unlikely that these parasites can be convicted. Henderson *et al.* (1942) reported a case of histoplasmosis of Darling in which the syndrome of ulcerative colitis presented, and they therefore stressed the importance of examination of stools for the presence of *Histoplasma capsulatum* in all cases. Many men in this field held with the late Sir Arthur Hurst, in England, and Crohn and Felsen, in this country, in the belief that ulcerative colitis is a form of chronic bacillary dysentery, the fact that *Shigella dysenteriae* cannot be uniformly cultured from the stools offering no embarrassment to this theory, since it is well known in the tropics that even in individuals with undoubted bacillary dysentery such culture is difficult after the acute stage is passed. Whether or not the disease is of infectious nature it certainly does not seem to be contagious, for Jackman's (1942) study of the records of 900 cases at the Mayo Clinic revealed occurrence in more than one member of a family in only 1.8 per cent of the series. Mackie's observations a few years ago led him to believe that complex deficiencies, not only in vitamins but in biologically complete proteins and in electrolytes as well, may constitute an essential part of the underlying mechanism of the disease. The possibility that allergic factors are important in the etiology has been presented by a number of independent observers. There is also considerable evidence of a psychogenic background in many of the cases.

THERAPY

Psychotherapy.—Nowadays the psychosomatic fellows are pressing in upon us from all sides. I personally feel that the situation is a somewhat dangerous one since in the best of us there is always the temptation to effect easy simplification by reduction of complex things to a common denominator. Therefore I have resisted the pressure which has been brought upon me to introduce a section on psychosomatic medicine in this book. However, there are certainly many situations in medicine in which it is utter folly to fail to envision a disease syndrome in terms of the patient as a whole, and there are undoubtedly many instances in which no progress whatever toward alleviation of the patient's condition can be made until both patient and physician frankly face the fact that symptoms and signs and even physical findings of a very concrete nature may be, however bizarre it may seem, the reflection of some sort of emotional disorientation. I do not know anything about this disease ulcerative colitis really, but it is certainly a recurrent and wasting disease of unknown etiology and there is much evidence in the experience of many men that

personality factors are important in its precipitation. Possibly a carefully taken psychosomatic history should be included in all cases of ulcerative colitis, with selection of suitable cases for psychotherapy—but of course that would be a most difficult thing for most men to do. Well then, perhaps a competent psychiatrist should see all of these patients early in consultation. Daniels, (1944) who has apparently examined quite a number of these cases psychiatrically in several New York hospitals, says that although general statements cannot be made that emotional factors are important in all cases, continued study shows that this is so in the majority. He says that frequently gross psychiatric disorders antedate the outbreak of the disease, that these patients are emotionally immature, that they frequently break at crises which represent a forward step in emotional sexual maturity such as engagement, marriage and childbearing, that financial difficulty and loss of a close relative are frequently important, that fixation on the mother is an outstanding feature, and that behind all this lies much repressed hostility which is often concealed in the symptoms. Daniels says that psychotherapy has been eminently successful in many instances, its application depending on the severity of the neurosis and the experience and equipment of the therapist. It is becoming increasingly important for us to understand what the psychiatrists mean when they employ these weird expressions and devious delineations.

Rest.—It would seem that all authorities, whatever their disagreement on other points, are unanimously of the opinion that the patient should be maintained at complete rest in bed so long as there is fever and more than two or three stools daily.

Diet and Vitamins.—Donald and Brown (1940), of the Mayo Clinic, said with regard to victims of this disease that one fundamental fact is certain: their chances for recovery depend greatly on the availability of the best possible quality of food. They found that protein is the most important article, chiefly in the form of red meats, liver, kidneys, sweetbreads and lean pork, and that since fruit and vegetables may add too much residue to the diet and increase the number of bowel movements, restriction of these articles requires the supplementary use of ascorbic acid and all the fractions of the B complex. Cheney (1939) reported the satisfactory initiation of remissions by the injection of liver extract as in pernicious anemia, believing that the effective factor is probably some as yet unidentified substance in liver. As a result of their exhaustive study of 37 patients, Bercovitz and Page (1944) came to the conclusion that the syndrome of chronic ulcerative colitis is not confined to an altered physiology of the colon but is also manifested by altered absorption and utilization, an impairment of the insulin mechanism, generalized decreased capillary resistance and altered blood coagulation by a decrease in prothrombin content. In some of their patients with rectal bleeding treatment with vitamin K caused a marked diminution in the hemorrhage. See chapter on the Deficiencies for methods of using all the vitamins.

Sulfonamides.—The record of these agents in ulcerative colitis is not very distinguished. One would of course expect the most from sulfaguanidine and sulfasuxidine, but there are no unqualifiedly favorable reports of even these two; some men find one or the other of them helpful in a certain proportion of their cases but in no case is there talk of cure, only symptomatic relief. The interested reader will find the following references in the bibliography: Collins (1940), Kraemer (1942), Kirsner *et al.* (1942), Stickney *et al.* (1942), Streicher (1943), Mills and Mackie (1943). Bargen (1944) said that so far in his experi-

ence azosulfamide seemed to be the drug of choice. Poth and Ross (1944) used phthalylsulfathiazole in a small series of cases and felt that this agent deserves further study.

Vaccines and Serum.—Believing that the majority of cases are the result of infection with dysentery bacilli, Hurst (1936) used polyvalent antidysentery serum. After preliminary desensitization 20, 40, 60, 80 and 100 cc. were injected intravenously on consecutive days; sometimes a few additional doses of 100 cc. were given. The experience of Crohn and Rosenak (1935) convinced them also of the superiority of this type of treatment at that time. Bargen has prepared a vaccine with the organism that he considers causative and has also used a serum prepared by immunization of the horse.

Diarrhea.—Early in all cases some attempt is usually made to control the diarrhea, though it is a fact that such success as rewards these efforts is nearly always only temporary. The following drugs are usually tried out in succession:

Bismuth subcarbonate, 20 to 30 grains (1.5–2 Gm.) every three hours.
Bismuth betanaphthol, 10 grains (0.6 Gm.) every four hours.
Calcium carbonate, 15 to 30 grains (1–2 Gm.) every four hours.
Calcium glycerophosphate, 10 to 15 grains (0.6–1 Gm.) every four hours.
Acetyltannic acid (tannigen), 3 to 10 grains (0.2–0.6 Gm.) every four hours.
Protan, 20 to 30 grains (1.3–2 Gm.) every two hours.

Colic.—During the course of a severe attack, hot stupes applied to the abdomen, according to the method described under Pneumonia, often bring relief; morphine, $\frac{1}{8}$ to $\frac{1}{4}$ grain (0.008–0.015 Gm.) or dilaudid, 1/48 to 1/32 grain (0.0013–0.002 Gm.), or preferably codeine, 1 grain (0.065 Gm.), may be needed; of course paregoric in usual doses could also be used. Hurst gave tincture of belladonna (laudanum) every four to six hours, increasing from 5 minims (0.3 cc.) to the maximum amount that can be taken without uncomfortable dryness of the mouth resulting. He found a tablespoonful of charcoal several times daily also helpful. Bargen and Jackman (1939) found that the addition of $\frac{1}{3}$ grain (0.02 Gm.) of papaverine hydrochloride to an opiate-atropine mixture is helpful.

Local Applications.—Attempt is often made, by means of antiseptic enemas or topical applications, to bring about healing of the ulcers; the details of such locally applied therapy are discussed in the article on bacillary dysentery. It should be remembered that the tissues are highly sensitive to trauma in colitis, and overloading with excessively large retention enemas should therefore be avoided, and the soft catheter should be introduced only just beyond the anal sphincter. Eyerly and Breuhaus (1938) followed a cleansing enema in one hour with a retention enema consisting of 3 to 5 ounces (90–150 cc.) of 3 per cent aluminum hydroxide and 15 per cent kaolin in colloidal suspension mixed with an equal amount of sterile distilled water, the patient retaining this as long as there is no discomfort. Best (1937) used daily rectal injections of 2 to 4 ounces (60 to 120 cc.) of cod liver oil.

Intestinal Oxygenation.—Felsen (1931–1936) studied the effects of altering the gaseous tension in the intestines by the rectal introduction of oxygen. Experience showed that the average acutely ill adult will tolerate 250 cc. (measured by water displacement as it comes from the tank) given alternate hours between 8 A.M. and 8 P.M. Passage through warm water heats the gas, which is then allowed to enter through an ordinary soft rubber catheter introduced only a few inches. There is moderate distention of the bowel as far as

the pylorus, but much of the gas is apparently rapidly absorbed since very little is ejected from the rectum. Felsen believed that this treatment leads to the diminution of spore-bearing anaerobes, encourages the superficial growth of obligatory or facultative aerobes, and favors a homogeneity of intestinal flora; the effect of oxygen on the intestinal tissue proper is even more speculative. Forty cases thus treated, with adequate controls, were apparently much benefited.

Calcium and Parathyroid.—Haskell and Cantarow (1931) used these drugs with satisfaction in 9 of 10 patients: calcium lactate, 30 grains (2 Gm.), or calcium gluconate, 60 grains (4 Gm.), orally three or four times daily, three and a half to four hours after meals, the patient being cautioned not to eat between meals; 20 to 30 grains (1.2–2 Gm.) of ammonium chloride were given with the calcium salt to increase its utilization by raising the hydrogen ion concentration of the tissues. Parathyroid extract was injected intramuscularly, 20 to 30 units, at intervals of forty-eight to seventy-two hours. Reporting again, in 1935, they said that 5 of the patients had remained essentially symptom-free for periods of two to six years; relapses occurred in 2 instances, but the patients again responded to the treatment; 1 patient died of pneumonia after remaining well for three years. In an additional 16 cases, treated for six months to four years, 8 became clinically well, 7 were much relieved, and 1 was not benefited.

Transfusion and Iron.—Several observers feel that blood transfusions have been of great value in many of their severely ill patients; Benson *et al.* (1942) said that at the Mayo Clinic they felt these chronic ulcerative colitis patients were more liable to transfusion reactions than ordinary postoperative or anemic patients. If he could get it, Felsen (1936) used to prefer to use the blood of a donor who was known to have recovered from bacillary dysentery. I do not know his present attitude in the matter. Many observers have found the administration of iron valuable also.

Allergic Factors.—Investigation from this standpoint should be worth while in all cases; Andresen (1942) found food allergy to be the principal cause of the ulcerative colitis in 33 of his series of 50 patients. However, Mackie (1942), while believing allergy to be very important, thought it often only a secondary factor, *i.e.*, a local sensitization developing upon a tissue previously inflamed through the operation of some other factor.

Surgery.—Ileostomy is sometimes a life-saving measure in severe cases, but the results are often poor and resort to the operation is furthermore surely a confession of defeat; Streicher (1942), in summarizing his own experience and that of one hundred specialists whom he consulted by questionnaire, stated the opinion that the operation should be performed only upon those patients in whom the colon has undergone irreparable damage. Bargen *et al.* (1943), in presenting a summary of experience at the Mayo Clinic, suggested that when it has become necessary to perform ileostomy the advisability of a subsequent colectomy should be seriously considered. Appendicostomy, or cecostomy, with subsequent daily washings for an hour (normal saline for twenty minutes, 1 to 2 per cent tannic acid solution for twenty minutes, normal saline for twenty minutes), is sometimes preferred. According to accounts I have read, some English surgeons recommend appendicostomy in almost every case, but the late Sir Arthur Hurst certainly deplored such routine surgery.

HEMORRHOIDS

Internal hemorrhoids are masses of redundant tissue caused by the dilatation of capillaries, arteries, or venules just inside the anal sphincter. They cause trouble either by reason of the fact that they are ulcerated and thus give rise to considerable pain when scraped by the feces, or by their bleeding, or by their prolapsing, which necessitates frequent manual replacement up behind the sphincter, or by the fact that they become strangulated after having passed out through the sphincter. The so-called "external" hemorrhoids are really only tags of skin that are vascular and that become troublesome when inflamed. A great deal of anal itching is usually associated with hemorrhoids. Smith's (1943) report of 3 cases of lymphosarcoma resembling internal hemorrhoids, and the discussion which followed the presentation of his paper, caution against the making of snap diagnoses of "piles."

THERAPY

Palliative Measures.—Prolapsed hemorrhoids are best sprayed with cold water, or a cold compress may be applied, in order to reduce the congestion; they may then be gently returned through the sphincteric canal by manipulation with the oiled fingers. Other palliative measures than this, I think, are no longer justified in view of the excellent results now to be attained by employment of either of the two curative measures; however, of the following prescriptions, the first is for an astringent rectal suppository, the effect of which can be modified by changing the proportion of tannic acid:

℞	Tannic acid	gr. xv	1.0
	Balsam of Peru	♏xxij	1.5
	Bismuth subcarbonate	ʒiiss	10.0
	Oil of theobroma (cacao butter)	ʒiv	16.0
	Cerate	ʒss	2.0

Make 10 suppositories.
Label: 1 three times daily.

And the second is for an analgesic suppository:

℞	Powdered opium	gr. vj	0.4
	Extract of belladonna	gr. ij	0.12
	Ethyl aminobenzoate	gr. xviij	1.2
	Oil of theobroma (cacao butter)	ʒiij	12.0

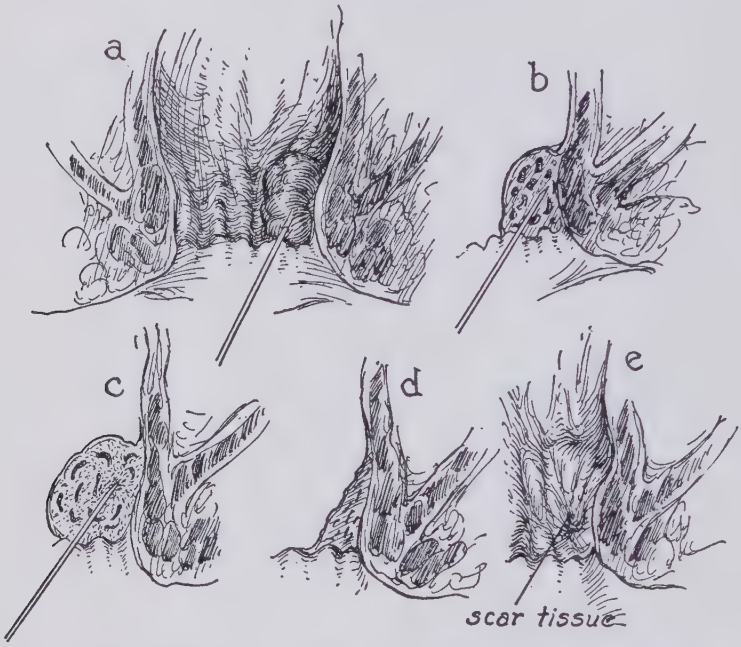
Make 6 suppositories.
Label: 1 before bowel movement.

For treatment of the itching see Pruritus Ani.

Surgery.—It is now urged by surgeons that internal hemorrhoids which are causing discomfort be removed by operation, a plea that is heartily endorsed by most nonsurgical practitioners since the operation is practically always successful, is not dangerous, does not incapacitate for a long period though the patient suffers much immediate postoperative pain, and oftentimes cures a stubborn constipation as well as the case of piles.

Injection.—External hemorrhoids must never be injected. It is now the consensus that the injection treatment may be employed with fair hope of affording relief to patients whose internal hemorrhoids are small or medium-sized and not accompanied by infection, thrombi, pain, muscle spasm, or marked prolapse. Bleeding is nearly always stopped, but in many instances the relief obtained through injection is not permanent. The patient presents

for treatment with the rectum empty, and during the period of the treatments should avoid the use of strong purgatives, obtaining a daily bowel movement by the use of mineral oil or a mild drug such as phenolphthalein if necessary. Enemas are not considered advisable while the treatments are being given. Haskell's (1939) technic seems to be about that which most men are nowadays employing: place the patient on the side in the Sims or a similar position and partially dilate the sphincter by inserting the finger before introducing a tubular anoscope of the Martin type. Usually 1 to 2 cc. of the sclerosing solution is injected through a long needle of small caliber, injecting one or two areas at a time and spacing injections about a week apart. The technic of employment of the solution is shown in the illustration below (reproduced through the courtesy of Dr. Neil W. Swinton, of the Lahey Clinic).



Technic of injecting hemorrhoids (Swinton, N. W., Surg. Clin. N. A., 19, 669, 1939): *a*, the needle inserted into the internal hemorrhoid, well above the anocutaneous line and deeply into the hemorrhoid; *b*, a cross section showing the tip of the needle in a perivascular position; *c*, the distention of the internal hemorrhoid; *d* and *e*, the resultant scarification.

Quinine and Urea Hydrochloride.—Perhaps this solution, popularized by Terrell, is still the one most often employed. For the average case 5 per cent strength is used, but 10 per cent is occasionally used in recalcitrant cases.

Phenol.—This agent seems to be greatly preferred in England and is also gaining favor in the United States. Swinton (1939) wrote that after a comparative study he favored it. The usually employed preparation is 5 per cent phenol in almond, olive, or cotton seed oil; Yeomans (1942) preferred oil of sweet almonds because he felt that the animal oils are absorbed too quickly and that mineral oil is not absorbed but remains as a foreign body.

Alcohol.—Alcohol seems to be preferred to anything else on the Continent, but it had very little vogue in our country because of the transient fever,

subsequent hemorrhages and occasional necroses which follow its use; some years ago Boas reported the practical elimination of these reactions through reduction in the concentration of the alcohol from absolute, or 95 per cent, to 70 per cent.

PROCTALGIA FUGAX

(*Spasmodic High Rectal Pain*)

Shortly before his untimely death, in 1936, Dr. Th. E. Hess Thaysen, of Copenhagen, recorded a series of cases of fleeting but severe rectal pain unassociated with other signs or symptoms, to which, with due apology for the philologic heresy of coupling a Latin adjective with a Greek substantive, he gave the name "proctalgia fugax." The flood of communications "to the editor" which followed the appearance of his paper, together with many conversations among physicians, have amply confirmed not only the existence but the frequent occurrence of this entity. The sufferers are usually adults and apparently more often males than females; there is no associated rectal or anal pathology, nor is there any evidence that the malady affects or is affected by intercurrent diseases, or that it shortens the duration of life. The victims merely suffer at varying intervals, oftentimes through a long series of years, fleeting attacks of excruciatingly severe pain whose site is practically always indicated to be within the rectum just above the anal sphincter. In his Croonian lectures on the visceral neuroses, in 1939, Ryle included mention of 15 cases of proctalgia fugax, and Lauda, in Vienna, reported a group of cases in the same year (not knowing, in fact, that the entity had been previously described). Apparently a large proportion of the 100 cases of high rectal pain which Buie and Brust analyzed, in 1934, were of this sort; it seems that MacLennan also described the condition as long ago as 1917. Characteristic features of an attack are the following: (*a*) Beginning often with a sensation of pressure high up in the rectum lasting a few moments, the pain develops rapidly to quite agonizing proportions, and then recedes slowly during several minutes; the average total duration is ten to fifteen minutes although attacks not infrequently last longer and now and then seem to be aborted before reaching full force. (*b*) The patient may gasp for breath and experience some degree of substernal tightness, but these manifestations seem to be not the rule; occasionally also there is sweating, pallor, and momentary loss of consciousness. (*c*) The pain seldom radiates and the attack is neither preceded, accompanied, nor followed by any disturbances of intestinal function (distention, tenesmus, constipation, or diarrhea). (*d*) An attack begins unaccountably at any time of day or night and seems to be unrelated to the state of rest or activity in which the patient finds himself at the moment. (*e*) Association with coitus, masturbation, migraine and epilepsy has been reported, but certainly in the majority of cases no such relationship has been established. (*f*) In the few recorded instances in which physicians have made digital examination of themselves during attacks, anal spasm has not been observed, and it has been noted by numerous patients that the stool may be passed with accustomed ease during an attack, though it is said that after defecation the pain sometimes seems to be accentuated in degree and extended in duration. (*g*) Bolen (1943) had the good fortune to be able to examine a

patient sigmoidoscopically during an attack. He found the rectal mucosa redder than normal, seemingly swollen, and the vessels prominent. The site of the pain was at the central portion of the levator ani muscle and slight pressure exerted by the tip of the instrument at this point caused mild spasm. The middle valve of Houston was more rounded than normal and the superficial vessels more pronounced. As the instrument reached the rectosigmoidal angle some difficulty was encountered in locating the lumen of the bowel, and at this point, with the passage of considerable amount of gas, the patient noted relief of the pain. As the sigmoid was approached, normal mucosa came into vision. Subsequent examination a week later revealed a normal rectum. (*h*) There may possibly be a familial tendency; at least Hurst (1943) reported that the father and younger sister of one of his patients suffered from exactly similar attacks. I expect that someday it will be suggested that these attacks may be bizarre epileptic equivalents.

THERAPY

There is really very little to describe for it is apparent that physicians, though well aware of the existence of this peculiar malady, have been treating it in the traditional fashion of the ostrich, both in themselves and in their patients. Perhaps now that it is brought out into the light and fully faced someone will give it the serious study it appears to deserve.

Local Treatment.—Of course the whole gamut of local measures—belladonna suppositories, hot applications, and so on—has been run, but with poor results. Both Marshall (1935) and Ryle (1939) have cited single instances of a patient who obtained quick relief through inflation of the rectum with air; I should think that this could be easily accomplished with the ordinary rubber bulb infants' enema syringe, usually at hand as a denizen of a dark corner in the bathroom medicine cabinet. Ryle (1944) also described the experience of a colleague who obtained relief through distention of the rectum with water.

Postural Change.—Thaysen recorded a patient who found it helpful to lie flat on the belly, another on the back, a third on the side; a fourth sat on the edge of a hard chair. Smith's (1935) patient was relieved by the adoption of a completely doubled-up squatting position with finger tips touching the floor; apparently the ordinary position of defecation does not provide sufficient flexion.

Allergic Factors.—It seems to me that it has taken the allergists a long time to learn that Thaysen has raised this condition to a position of respectability since there would seem a fair chance that they might reasonably claim it for their own. Several years ago Bramigk (1935) obtained relief in 2 cases by use of Rowe's elimination diets.

Tobacco.—Several years ago I recorded a case in which, arguing the analogy between these attacks and those in "pseudo" angina pectoris, the patient was required to stop smoking with resultant complete relief. Ryle (1939) seems to investigate the smoking habits of his patients, but records only one instance in which the patient stopped smoking; other adjustments were made in this patient's life at the time, but it is noteworthy that the attacks ceased to occur. However, proctalgia fugax also occurs in nonsmokers.

Amyl Nitrite.—Marshall's (1935) patient obtained as certain, quick and complete relief from amyl nitrite as does the angina sufferer. "A few seconds with a capsule and a handkerchief at the side of the tennis court, or in the cloak room at a dance, and all is well and he can rejoin his party."

Benzedrine (Amphetamine).—Oderr's (1943) patient was almost instantly relieved by the use of the benzedrine inhaler. The patient was at the time in a state of premenstrual tension and had had a very fatiguing day.

EPIDEMIC VOMITING AND DIARRHEA

(*Acute Infectious Gastro-enteritis; "Intestinal Influenza"*)

Increasingly in recent years there have been reported outbreaks of an apparently infectious and contagious acute gastro-intestinal malady usually referred to colloquially as "intestinal flu." I have seen reports of these epidemics in England and on the Continent as well as in the United States; most probably they occur elsewhere also. Usually the epidemic appears and disappears rather suddenly but may persist at its peak in a given locality for several weeks. The number of cases is often very high, as for example here in Milwaukee in the spring of 1936, when it was thought we had more than 100,000 cases—I doubt the figure, but at any rate a good many people were sick with this malady at about the same time. Fortunately, the mortality is very low; indeed the primary mortality seems to be practically nil. The characteristic symptoms are sudden onset of nausea, vomiting, abdominal cramps, watery diarrhea, slight headache and general aching, weakness, some fever, and a general feeling and often appearance of a considerable degree of prostration. In various outbreaks one or other of the symptoms seems to predominate; for example, there is sometimes considerable vomiting without diarrhea, while at other times abdominal cramps and profuse and debilitating diarrhea are seen to the exclusion of most of the other symptoms. Some patients are afebrile, others have grippal symptoms. In most instances the duration seems to be between two and five days, recovery occurring quickly and without sequelae; relapses and second attacks, however, are of frequent occurrence.

No organism has been consistently recovered from any of the excreta and identified in a probable causative role in this disease. Here in Milwaukee, as elsewhere, we have indulged in a certain amount of discussion of a possibly contaminated water supply, but nothing definite has come of this. There are of course those who hold that the disease is of virus origin and that infection occurs by the droplet route, but their case is by no means established either.

THERAPY

No specific therapy is at hand of course. In fact, since the condition is self-limited it does not seem to me sensible to attempt to do a great deal more than merely wait. Several years ago, Wildman (1933) said that milder cathartics are not effective, that magnesium sulfate and mineral oil both aggravate the condition, but that castor oil in full dose in the beginning might be helpful—he said actually that he found "no drug to compare with castor oil" but he did not specifically say to compare with it for what; presumably general relief of the whole distressed state was meant. He also liked to give a cleansing saline enema and, if there is much nausea or vomiting, to precede the castor oil and enema about fifteen to thirty minutes by 1/100 to 1/50 grain (0.0006 to 0.0012 Gm.) of atropine sulfate hypodermically.

Greenthal (1936), discussing his experience of cases among children here in Milwaukee, said he knew of no measure which will relieve the severe vomiting in the beginning, but total abstinence from food and water for a few hours is probably advisable; however, if fluid is desired he allowed a few sips at a time of water, weak tea, carbonated beverages, cereal gruels and fruit juices, but not milk or broth. Heat to the abdomen is often very soothing, and of course after sufficient time has elapsed so that one is certain he may not mask a more serious abdominal disorder, paregoric or even the stronger opiates may be used if still needed. After subsidence of the more acute symptoms, Greenthal placed his children on a high carbohydrate diet —omitting milk, eggs, meats and soups and giving sugars and starches freely—and found that the diarrhea usually responded promptly to this regimen. In some cases he used the apple diet (see Index) with good results. Return to milk must be postponed for some time as it seems often to cause a relapse.

DISEASES OF THE LIVER AND BILE PASSAGES

JAUNDICE

In approaching jaundice differentially it should be remembered that almost all the types of liver and bile duct disease may produce jaundice with little or no pain. Chronic pancreatitis, carcinoma, hemolytic jaundice and several of the other anemias, familial nonhemolytic jaundice and Weil's infectious jaundice are to be ruled out. Eppinger (1937), and more recently Kirschbaum and Popper (1940), have described a few cases of a fulminating fatal form of toxic hepatitis which appears to be an intermediate stage between acute infectious hepatitis (catarrhal and human serum jaundice) and acute yellow atrophy. In lobar pneumonia, jaundice is probably always latent but may appear clinically; it may sometimes be seen in relapsing fever, in congenital or acquired syphilis, in sepsis and tuberculosis, and it is often present in malaria and always present in yellow fever. Many chemical poisons may cause toxic hepatitis and jaundice: arsenic, antimony, acetic acid, carbon tetrachloride, cinchophen, chloroform, dinitrophenol, phenylhydrazine, potassium chlorate, phosphorus, picric acid, snake venom, mushroom poison, trinitrobenzene, tetrachlorethane, trinitrotoluol. Jaundice may appear in eclampsia and following accidental or operative trauma; it may arise from any one of a number of mechanisms in chronic heart disease (its sudden appearance in myocardial insufficiency points toward pulmonary infarction); and it is one of the symptoms following the transfusion of incompatible blood.

Jaundice recurring with each menstrual period is said by Lichtman (1942) to have been reported in a few individuals; Drenckhahn (1943) reported a case of jaundice associated with giardial infestation, both the infestation and the jaundice disappearing quickly under atabrine therapy; and Crawford (1944) reported jaundice in a severe case of meningococcal sepsis, all symptoms including the jaundice clearing rapidly under sulfonamide therapy. The ordinary icterus neonatorum is physiologic, being a reflection of the presence in the blood of an increased amount of bilirubin resulting from hemolytic destruction of surplus erythrocytes; the etiology of the rare and fatal Winckel's disease is still unknown; icterus gravis neonatorum (erythroblastosis foetalis) has been the subject of a great deal of study in recent times and the significance of Rh negativity in the blood of the mother and Rh positively in the blood of the affected infant has been thoroughly elucidated.

Such of the above entities as come within the province of this book are taken up at sites too numerous to list here; the reader is referred to the table of contents and the index. But when all of these have been differentially ruled out there remains a type of case formerly generally designated "catarrhal jaundice" but in the light of relatively recently acquired knowledge more accurately described as "acute infectious hepatitis"; under the latter designation the entity will be discussed below, and a timely subject it is in view of the extent to which this disease incapacitated large numbers of our troops during War II.

ACUTE INFECTIOUS HEPATITIS

(Catarrhal and Human Serum Jaundice)

As commonly encountered this malady is mildly epidemic in children and in young adults and occurs more often in males than in females; however, middle aged and even elderly patients are not infrequently seen. But in times of war it has often been recorded in major epidemic form during the past hundred and fifty years. In circular letter No. 95 from the Surgeon General's Office, September 5, 1942, it was stated that in the first year of the Civil War there were 10,929 reported cases among Northern troops. The French have referred to the disease as the "Jaundice of Camps" and the English have often called it the "Jaundice of Campaign." In War I there were 2195 cases in British troops in the Mesopotamia and Dardanelles region in the fall of 1915, and in War II it was epidemic among the British and German troops in the desert campaign in Africa and in troops of the United Nations in the Middle East and in India; indeed, Witts (1944) said this disease provided one of the major medical problems of the war in the Mediterranean area. It has also been reported occasionally in association with the employment of measles and mumps convalescent serum, of glycinerated humanized smallpox lymph and of reconstituted human adult serum and plasma. And in 1942 we had in the American Army an enormous number of cases associated with the employment of yellow fever vaccine in the preparation of which human serum had been used; the absence of cases in the Navy was due to the fact that by unusual chance none of the icterogenic lots of vaccine was received by them. Dietary indiscretions, the abuse of alcohol, and exposure to cold were often formerly mentioned in the etiology of this type of hepatitis in the past, but its infectious nature has now been definitely determined by the following evidence: (*a*) the epidemic distribution of the cases; (*b*) Marchand (1943) recounted that in an isolated Indian village in the Yukon territory brought into contact with the outside world by the construction of the new Alaskan military highway, epidemics of measles, dysentery, whooping cough, mumps, meningococcal meningitis *and* infectious hepatitis broke out among the inhabitants; (*c*) the production of the disease in human volunteers (Findlay and Martin, 1943) by instilling into the nares nasal washings from patients down with the disease, and by the inoculation of serum (Oliphant, 1944) from individuals previously inoculated with icterogenic lots of yellow fever vaccine; (*d*) the strongly presumptive experimental (Havens *et al.*, 1945) and practical field (Kirk, 1945) evidence that the causative agent is present in human excreta, probably principally in the feces.

It was the conclusion of Findlay *et al.* (1944), after a thorough study of the matter, that the two entities, acute infectious hepatitis and human serum jaundice, are caused by the same or very closely allied agents.

The symptoms of acute infectious hepatitis (perhaps it would be better to refer to the entity as epidemic hepatitis) are malaise, sometimes mild headache and dizziness, enlargement of the liver and sometimes of the spleen, occasionally pain in the liver region, nausea and perhaps vomiting—both these latter symptoms being especially marked if the patient refuses to go to bed—slight fever, or normal or subnormal temperature, slow pulse, jaundice, bile-stained urine and clay-colored stools, more or less general pruritus, and mental depression which is sometimes quite profound and is not infrequently associated with an unwonted irritability. The gastric symptoms usually

persist for only a few days, but many patients suffer a return of nausea and dizziness if they attempt to assume the upright position at any time throughout the course of the malady. The duration of an attack is from ten days to three or even six weeks, and some degree of jaundice often persists for a long time in a patient otherwise apparently quite recovered. Occasionally the attack recurs. In the independent studies of cases in the Army in widely separated geographical areas, Turner *et al.* (1944) and Sawyer *et al.* (1944) found a case fatality of approximately 3 per 1000. Caravati (1944) reported that he had seen a rather large group of officers and enlisted men who, as an apparent sequel to jaundice contracted in the Army in 1942, exhibited a clinical syndrome which he designated "posthepatitis syndrome," the principal findings being fatigue, right upper quadrant discomfort, digestive disturbances particularly fat intolerance, malnutrition and emotional instability. One wonders whether these are not just the findings that might be expected in many psychoneurotic individuals after a long confining illness.

Until recent times it has been rather the custom to look upon this malady as the result of a gastro-enteritis with a "catarrhal" condition of the mucosa of the upper gastro-intestinal tract and the bile ducts and with the ampulla of Vater plugged with mucus, this conception being, in the words of the author of an editorial in the Lancet (April 8, 1944), "one of Virchow's less fortunate contributions to pathology." Recently, however, the biopsy studies of Roholm and Iversen (1939) in Sweden, amplified and extended by Dible *et al.* (1943) in England, established the fact that there is really an hepatic lesion in these cases. The material obtained by these workers through aspiration of a small cylinder of liver tissue from individuals sick with infectious hepatitis revealed degenerative necrotic or autolytic changes in the hepatic cells especially in the center of the lobules. Repetition of the biopsies after recovery showed complete restitution in some cases but in others some degree of atrophy and occasionally mild fibrosis or cirrhosis. There were no evidences of bile stasis as required in the older concept. Upon autopsy in fatal cases, Lucké (1944) found in the liver without exception the changes typical of idiopathic yellow atrophy.

From a study of the liver function of 36 persons who had had attacks of infectious jaundice one to twenty-nine years previously, Altschule and Gilligan (1944) concluded that a mild benign form of chronic hepatitis is frequent after recovery from the acute attack; however, Lucké (1944) found complete restoration of hepatic parenchyma in 14 individuals who recovered and later died of some other cause.

In epidemics, unassociated with the administration of human serum, in the United States and in England, Norton (1939), Pickles (1939), Cullinan (1939) and McLeod (1944) found the incubation period to be between twenty-one and forty-five days. Cullinan, however, said that Glover, who made a considerable study of this disease, felt that the incubation period might be in some instances no longer than four days. Pickles proved contagion on the fifth and seventh days and thinks there is some evidence of contagiousness before the onset of symptoms. Gowen (1945), who studied 400 cases in Tunisia during War II, observed incubation periods of seven to thirty-eight days and he too felt that the disease was most highly communicable during the prodromal stages preceding the onset of jaundice. Both Pickles and Cullinan have acted successfully on the assumption that two weeks' isolation is sufficient in children; the latter did not hesitate to admit adult patients to

general wards when jaundice is once established. In cases associated with the administration of human serum the incubation period has been longer; it varied from forty-five to 104 days in the 71 patients of Bradley *et al.* (1944). However, in 6 of the 9 experimental cases of the serum type of the disease in human volunteers of Neefe *et al.* (1944) the onset of the disease occurred twelve to thirty-five days after inoculation, though it was said that several of these cases would not have been detected if liver function studies had not been carried out at frequent intervals.

THERAPY

Diet.—A light soft diet high in carbohydrate and adequate in protein but practically devoid of fat is usually prescribed. Toast, gruels, junket, custards, rice pudding, cereals, fruits and vegetables are all permitted in small quantities. Meats and cheese may be taken but only skimmed milk should be permitted, though as a matter of fact Havens (1944) reported that in the treatment of his 200 cases fats were withheld only when patients were unable to tolerate them. Hartfall (1944) warned against the use of alcohol in any quantity whatsoever.

Dextrose-Saline.—In describing the handling of a large series of cases in the British Middle East Forces in 1943, Gordon stated that when vomiting was frequent excellent results followed the administration by intravenous drip of a few pints of physiologic saline solution containing 5 per cent of dextrose.

Drainage of the Gallbladder.—It was formerly the general practice to start off with a dose of calomel and then to keep the bowel open with a daily saline purge, the idea being of course that the cathartic salts tend to cause opening of the sphincter of Oddi and reflex contraction of the gallbladder. But for a bedridden patient, who is not obtaining great quantities of food, large doses of salts are necessary to induce defecation, and the evidence that much biliary drainage is accomplished in this way is not convincing. Furthermore, in the light of our present understanding of the pathology of this disease, this sort of thing seems irrational.

Another sort of therapy the worth of which I very much doubt is the attempt to improve biliary drainage through provoking an alteration in mucous membrane secretion by the use of ammonium chloride in about 7½-grain (0.5 Gm.) doses, as in the following prescription.

℞	Ammonium chloride	ʒiv	15.0
	Syrup of citric acid	℥j	30.0
	Water to make	ʒiv	120.0

Label: Teaspoonful in water three times daily after meals.

Nonsurgical drainage of the gallbladder (Lyon duodenal tube method) has often been said to be of value by the devotees of this procedure, but Havens (1944) performed it in 90 of his 200 patients without observing any indications that it was beneficial.

Local Analgesia.—Hot applications over the liver region are felt to be of value in some cases; perhaps fomentations (stupes) are sometimes to be preferred to the hot water bag, but it seems needlessly hectic therapy to force this sort of thing upon the family attendant when the patient is no more dangerously ill than is usually the case in infectious hepatitis.

Miscellany.—Some physicians still give calcium salts but probably without effect. Bile salts, since they are usually not present in very large quanti-

ties in most cases (witness the clay-colored stools), are rationally employed, more especially as recent work is showing that certain of the vitamins are poorly absorbed in the absence of bile. The vitamins themselves are also indicated. Breese and McCoord (1940) showed that vitamin A is poorly absorbed in infectious hepatitis, and there is also evidence that vitamin B complex improves liver function. Of course if there is some tendency toward bleeding, or perhaps even if not, the indication exists for the administration of vitamin K. The methods of employing all the vitamins are discussed elsewhere in the book (see Index). Relief of itching is discussed under Portal Cirrhosis. Havens (1944) employed sulfonamides in 7 patients apparently without effect.

PROPHYLAXIS

During an epidemic of infectious hepatitis in a summer camp for children, Stokes and Neefe (1945) injected gamma globulin intramuscularly and obtained results which they thought indicated that this agent will prevent or attenuate infectious hepatitis to a degree comparable to that observed when it is used in measles. Further trial of this method of prophylaxis will be awaited with interest.

BLEEDING IN OBSTRUCTIVE JAUNDICE

(*See Vitamin K Deficiency*)

THE CIRRHOSES

The study of the cirrhoses of the liver has only recently been taken up again with vigor after having been neglected for a very long time. Anyone, therefore, who writes upon the subject today must do so with the knowledge that tomorrow, or perhaps the day after, all that he has to say may be shown to be quite wide of the truth, for much has been learned in recent years. "The subject is ripe for investigation," says Rowntree; "it awaits the touch of a Richard Bright." But, pending the arrival of the new Bright, I must content myself with a more or less conventional listing of the entities.

The cirrhoses, then, may be divided into (*a*) portal, (*b*) syphilitic, (*c*) Hanot's, (*d*) obstructive biliary, and (*e*) cardiac. Of these types, it may be said that Hanot's, if it really exists as a disease entity, is of so rare occurrence that it cannot be dealt with in this book (the same statement regarding rarity applies also to Banti's disease, Wilson's disease and hemochromatosis, in all of which cirrhosis forms a part of the picture). The syphilitic affections of the liver are dealt with in the article on Syphilis; it should be noted, however, that portal cirrhosis may occur in an individual who also has syphilis, *i.e.*, every case of cirrhosis in a syphilitic is not necessarily a case of syphilitic cirrhosis. Obstructive biliary cirrhosis occurs as a complication of chronic gallbladder disease, and is relieved or not accordingly as the measures directed toward the cure of the gallbladder condition succeed or fail; or it may result from congenital deformities in the bile system; also there is an infantile form of biliary (or portal?) cirrhosis apparently peculiar to certain regions in

India and thought likely to be a reflection of dietary deficiencies in the mother. "Cardiac" cirrhosis is the term applied to describe the state of diffuse fibrosis with some alteration of architectural pattern sometimes seen in livers which have been the seat of prolonged and advanced passive congestion as a result of heart failure. Koletsky and Barnebee (1944) said that the clinical aspects of cardiac cirrhosis do not provide adequate data for antemortem diagnosis, but Garvin (1943) stated that the diagnosis had been suspected in 5 of the 35 cases whose clinical and autopsy findings were studied by him. Portal cirrhosis, then, alone requires separate consideration, which it is given in the section below.

PORTAL CIRRHOSIS

The clinical entity which we recognize as portal cirrhosis results from prolonged inflammatory, degenerative, or proliferative changes in the liver, which are believed to occur in the following sequence: (*a*) degeneration of cells in the periphery of the lobules, (*b*) proliferation and contraction of interstitial tissue about the remaining cells and the bile ducts, which attempt repair by means of a resort to hyperplasia, and (*c*) portal obstruction and the more or less successful attempt to overcome it by the establishment of a collateral circulation. The surface of the liver is usually "hob-nailed" and the organ diminished in size, but it may be enlarged and smooth due to the deposition of fat. The spleen is also frequently enlarged, whether merely by reason of venous congestion or because the liver is not an isolated organ but exists as part of a "splenohepatic" system, is not known. Infections, toxins, overactivity of the liver, excessive deposition of pigments, nutritional deficiency—any one or all of these, or perhaps of other as yet unsuspected factors, may be the causative agent in a given case. Bloomfield's (1938) opinion, based upon considerable study of cases over a period of years, is one in which most clinicians undoubtedly concur; to wit, cirrhosis is usually the terminal stage of a long disease which runs most of its early course without clinical symptoms. Excessive use of alcohol has long been blamed for the production of most of the cases, but Mallory (1933), who investigated the matter both clinically and experimentally for many years, was of opinion that it might be phosphorus as a contaminant, rather than alcohol itself, which causes the disease. Von Gerlach (1935) found the copper content of cirrhotic livers relatively high and thought that this mineral in conjunction with alcohol might be of significance in the causative role. Moon (1934), reviewing the literature, found that a rather large number of substances may induce experimental cirrhosis; very interesting, from the clinical standpoint, is the fact that nicotine may be one of these. Boles and Clark (1936), studying the records of 4000 autopsies at the Philadelphia General Hospital, concluded that alcohol is not a specific causative factor, and Boles, in 1943, reiterated the viewpoint. However, Evans and Gray (1938) deduced from the cirrhosis records among more than 17,000 autopsies at the Los Angeles County Hospital that "the excessive consumption of alcoholic beverages seems to be a contributing factor." Connor (1939) felt there could be little doubt that alcohol and the habits induced by the consumption of large amounts of alcohol are the most important factors in the production of fatty liver which passes on in some cases into cirrhosis; his studies indicated that the factor next in importance to alcohol itself is the abnormal diet which invariably accompanies severe chronic alcoholism, and he felt that one might

further reduce this to a specific lack of sufficient carbohydrate in the diet. Hall and Morgan (1939) gave their opinion as follows, as the result of careful study of a considerable series of cases in which alcoholism was the most common clinical factor: "The patient with chronic alcoholism suffers from low intake of carbohydrate, greatly diminished storage of glycogen, fatty replacement of the liver, and deficient intake of vitamins. These conditions render the liver especially vulnerable, so that continued abuse of alcohol is followed by necrosis of liver cells and fibrosis, which in the susceptible patient after years results in cirrhosis. We believe that in the majority of cases the enlargement and fatty infiltration of the liver constitute the first development, that this passes imperceptibly into the subacute phase of cirrhosis, to be followed later, if the patient survives long enough, by the appearance of the small hobnail liver. A small percentage of the patients die during the subacute stage as a result of complicating infections, dietary deficiency diseases, hepatic insufficiency, portal hypertension, alcoholic psychoses, and other disorders. We believe the term 'alcoholic cirrhosis' has a firm basis in etiology." The studies of Patek and others in recent years are certainly pointing toward definite vitamin A and B-complex deficiencies in so-called alcoholic cases. However, cirrhosis does also undoubtedly occur among nondrinkers, not only alleged nondrinkers in regions of high alcohol consumption, but likewise among peoples who do not drink at all, as was shown by Yenikomshian (1934) and Stacey (1944) with regard to the nondrinking populace of Syria, the Lebanon and Iraq, and by others for several of the Far Eastern peoples. Attempts to correlate statistically a rise or fall in cirrhosis incidence with the alcohol-prohibitive measures that have been tried out in various parts of the world are worthless, all countries having explicitly or tacitly admitted that such measures notoriously fail to control alcohol consumption. It has been alleged that beer is less prone to cause cirrhosis than wines and "hard" liquors. There the matter stands—still controversial, but it seems to me that the supporters of the alcoholic side of the argument are beginning to win again.

Portal cirrhosis occurs most frequently in the early forties and terminates fatally in the early fifties. Men are more frequently affected than women in about the proportion of 2 or 3 to 1. In their very thorough analysis of 386 cases, Ratnoff and Patek (1943) found an increased incidence in patients of Italian and Irish stock but no convincing evidence of hereditary predisposition; Karsner's (1943) study indicated that Negroes are somewhat more susceptible than whites. The early symptoms are dyspeptic and are rarely recognized, though the new tests of hepatic function should make diagnosis easier now than it was a few years ago; parenthetically, however, one should note that Watson (1944) and his associates at the University of Minnesota, who are studying this matter intensively, believe that the concomitant employment of several types of test is necessary in order to obtain information of value. In a fully established case the patient has lost much weight and energy, has a muddy complexion, sunken eyes and a sharp nose on which there are distended venules; he complains of dyspepsia and perhaps of hemorrhoids and of an intensely itching skin. Engorgement of the veins in the abdominal wall and elsewhere is a striking evidence of the attempt that is being made to establish a collateral circulation. Ascites occurs in more than 50 per cent of cases, the abdomen sometimes containing as much as 15 liters of fluid. Both the spleen and the liver may be found to be enlarged. The urine is

usually scant and highly colored; in some cases there is a pernicious-like anemia. Purpura and a tendency to easy bleeding are very common, and profuse hemorrhage from the stomach, due to the anastomoses formed about the lower end of the esophagus, is a frequent and serious occurrence. The statistical study of Ratnoff and Patek (1942) indicated that in addition to hematemesis the appearance of jaundice and ascites are ominous prognostic signs. In far-advanced cases such symptoms of hepatic insufficiency as malaise, nausea and vomiting, headache, depression, loss of memory, and delirium or coma may be seen. The majority of patients do not die from hepatic insufficiency directly but from the complicating disorders, such as circulatory failure, hemorrhage, ascites, and intercurrent infectious disease, particularly pneumonia or a rapid tuberculosis.

John Brown described a case of cirrhosis in 1685; John Andre in 1788, and Matthew Baillie in 1818, both wrote on the subject; but the first adequate account was that of Laënnec, who gave the disease its name in 1819.

Therapy

Diet and Vitamins.—The production of cirrhosis in experimental animals by dietary alterations is now accepted fact but of course such deliberate studies cannot be performed in the human; nevertheless there is now ample pragmatic evidence that in man at least amelioration of symptoms can be effected by the institution of dietary measures. Numerous observers have reported good results with a new diet but I shall report here the methods and results obtained by Patek (1943), with whom this work began a number of years ago. The new diet constitutes a marked departure from the high carbohydrate and low protein and fat diet which has been so long used in treatment of the disease, since it comprises a diet which is very rich in protein and ample in both carbohydrates and fats. Patek's diet contains 3591 calories in the following proportions: protein 139 calories (including the protein in brewer's yeast), fat 175 calories, carbohydrate 365 calories. It employs principally meat, milk, eggs, fruit and green vegetables. Meat is served twice daily, milk five times daily—three times with meals and two times with 25 grams of powdered brewer's yeast. It is usually found advisable to feed the yeast in graded increasing doses up to the final amount; for the occasional patient who cannot tolerate brewer's yeast oral vitamin B complex must be substituted in the form of liquid yeast concentrates. In addition, thiamin chloride (5 mg.) is injected intramuscularly daily and liver extract (5 cc.) twice weekly. All who use these diets remark that the task of getting this much food into the patient is very difficult because the individual with cirrhosis often finds food loathsome. The diet chart of Patek and Post, altered by the omission of a semiliquid diet which they also included for use in exceptional cases, is presented in Table 22. The reader will find charts of food values in the article on Diabetes.

Patek's experience, since amplified by him and confirmed by others, is the following: two months were required on the average before definite improvement became apparent, but at the end of the first year the survival rate was 57 per cent in a group in which this treatment was given as compared to 39 per cent in the group treated by older methods; at the end of the second year 45 per cent of the patients had survived as compared to 21 per cent who were not treated in this new way.

At the Mayo Clinic, Butt and Snell (1942) have also been giving large

amounts of vitamins A and B in the form of concentrated fish liver oil to their patients. Broun and Muether (1942) and Russakoff and Blumberg

TABLE 22.—CIRRHOSIS DIET (AFTER PATEK AND POST)

	Amount.	Proteins.	Fats.	Carbo-hydrates.
Breakfast				
Fruit 18%	1 serving			18
Cooked cereal or	200 grams	4	2	20
Prepared cereal	30 grams			
Sugar on cereal	12 grams			12
Eggs	2 only	13	10	
Milk	200 cc.	6	8	10
Toast	60 grams	4	1	30
Butter	20 grams		17	
Coffee				
Cream 20%	30 cc.	1	6	1
Sugar	12 grams			12
9 A.M. Brewer's yeast	25 grams	12.5	0.5	8.5
Milk	150 cc.	4.5	6	7.5
Sugar	12 grams			12
Dinner				
Meat, medium fat	100 grams	17	20	
Vegetables 5%	100 grams	1		4
Vegetables 10%	100 grams	2		9
Vegetables 20%	100 grams	3		19
Bread	30 grams	2		15
Butter	20 grams		17	
Dessert (cake, pudding)	1 serving	5	8	25
Milk	200 cc.	6	8	10
Coffee				
Cream 20%	30 cc.	1	6	1
Sugar	12 grams			12
2 P.M. Brewer's yeast	25 grams	12.5	0.5	8.5
Milk	150 cc.	4.5	6	7.5
Sugar	12 grams			12
3 P.M. orange juice	200 cc.			18
Supper				
Soup (Julienne)	200 cc.	4		4
Meat, medium fat	100 grams	17	20	
Vegetables, 5% salad	100 grams	1		4
Vegetables, 20%	100 grams	3		19
Bread	30 grams	2		15
Butter	20 grams		17	
Milk	200 cc.	6	8	10
Fruit 18%	100 grams			18
Tea				
Cream 20%	30 cc.	1	6	1
Sugar	12 grams			12
7 P.M. Milk	200 cc.	6	8	10
Grand total		139	175	365
	Calories 3591			

(1944) have reported favorable effects from the administration of choline in small numbers of patients, the agent being given for its lipotropic effect on

the supposition that the deposition of fat precedes irreversible fibrotic changes in some types of portal cirrhosis; in the cases of the latter authors the choline chloride was given by mouth in daily dosage of 2 to 6 Gm. divided usually between four doses. Yater (1943), however, expressed dissatisfaction with choline on the basis of its employment by him in about 15 cases; so we must wait to see what comes of further work.

Replenishment of Blood and Proteins.—See the discussion of anemias of this type in the chapter on the Anemias. Transfusion is often resorted to in cirrhosis not only for its temporary restoration of erythrocytes but also because it replenishes to some extent the depleted supply of plasma proteins. Fagin *et al.* (1943) reported remarkable results following the parenteral administration of amino acids in a small series of patients; further extension of this work will be awaited with interest. Greene (1943) injected ascitic fluid intravenously experimentally in some patients with results that were described as apparently partially satisfactory.

Iodides.—Iodides are often employed, as in the treatment of syphilis, in the hope that the overgrowth of connective tissue might thus be corrected, but I do not know that the survival of this practice rests upon any more secure footing than the rather vague clinical impression that it is of some value. It is of course an extremely difficult matter to put to the test of controlled clinical experimentation.

Focal Infection.—It is generally agreed that all demonstrable foci of infection should be eradicated if this can be accomplished consistently with the safety of the patient; that such treatment serves to arrest the progress of the disease can rarely, if ever, be shown, for whatever contribution the infectious process may have made toward the establishment of the disease has become accomplished fact long before the diagnosis of cirrhosis is made.

Dyspepsia.—In the beginning of the chapter on the gastro-intestinal diseases are discussed measures for the treatment of dyspepsia; they nearly always fail when instituted for the control of the dyspepsia accompanying cirrhosis of the liver, the reason being that such dyspepsias are due to congestion throughout the gastro-intestinal tract and that they are relieved only when the congestion is made to decrease, *i.e.*, when the cirrhotic process is abated or arrested.

Itching.—Sponging, not rubbing, with a hot solution of sodium bicarbonate followed by dusting with talcum powder, or the application of 1 per cent menthol in alcohol, or an ointment of 1 per cent phenol, may be tried. One of the calamine lotions, or the oatmeal bath (see in Eczema), is helpful to some individuals. Sometimes sweating brings relief, either induced by applied heat or the use of pilocarpine nitrate: 1/10 to 1/5 grain (0.006–0.012 Gm.) by mouth or hypodermically, repeated so as to maintain mild diaphoresis; in some individuals aspirin (acetylsalicylic acid) will produce as much sweating with fewer side actions. Lichtman reported, in 1936, that since his introduction in 1931 of the use of ergotamine tartrate in cases of intractable itching, he had obtained relief in about half his 75 cases; numerous other observers have also used the drug with satisfaction: ergotamine tartrate (gynergen), 1/60 grain (0.001 Gm.), three times daily by mouth, or subcutaneously or intramuscularly once a day in a dose of 1/60 to 1/20 grain (0.001–0.003 Gm.). But one must not overlook the potential toxicity of this drug; see under Migraine. Prinzmetal (1934) used the nitrites with satisfaction, giving amyl nitrite, nitroglycerin, or erythrol tetranitrate just as in

angina pectoris. In the experience of Rowntree and many others, calomel has proved the most effective agent; it is used in doses of $\frac{1}{4}$ to $\frac{1}{2}$ grain (0.015–0.03 Gm.) hourly for four doses a day (omitting the usual saline) for periods of three or four days. Sodium thiosulfate is also sometimes antipruritic when given intravenously in a dose of $7\frac{1}{2}$ to 15 grains (0.5–1 Gm.), to be repeated as necessary. Insulin in small dosage, without accompanying dextrose, has been said to be helpful in a few cases; calcium salts may also be worth trying.

Hematemesis.—Attempt should be made to maintain a normal prothrombin time by the administration of vitamin K (see methods in chapter on Deficiencies); but this is often difficult in advanced cirrhosis because the liver becomes unable apparently to form prothrombin even though an adequate supply of vitamin K is at hand. For the treatment of gross hemorrhage from the stomach, see Peptic Ulcer. Checking of bleeding from esophageal varices is approached by ligation of the coronary veins of the stomach or resort to the other surgical procedures mentioned later; recently, Walters, Moersch and McKinnon (1940) of the Mayo Clinic reported the successful sclerosing injection of these varices in six cases. Drenckhahn (1939) felt that it should be possible in each case to determine the level at which blood viscosity reaches a point at which flow through the liver is hindered and strain upon the collaterals becomes great enough to produce hemorrhage; having determined the level—in terms of hemoglobin percentage and erythrocyte count—at which the patient habitually bleeds, he would have a venesection of several hundred cubic centimeters performed for the following principal reasons: (*a*) spontaneous hemorrhage with its psychic shock is prevented; (*b*) the quantity of blood lost may be regulated; (*c*) general health is improved when the blood count is kept at a more nearly constant level; (*d*) the blood withdrawn can be used for transfusion. Drenckhahn reported 1 case apparently very satisfactorily handled according to these principles.

Ascites.—*Paracentesis.*—Soon or late all cases have to be tapped. The tapping is a procedure which it were idle to attempt to describe here since its technic can only be learned in the clinic. The indications, however, are another matter; they are well stated by Kern.

"Tapping should not be delayed so long that serious displacement of the diaphragm and excessive intra-abdominal tension have occurred. Something might perhaps be said in favor of the possible usefulness of moderate effusions as promoting the development of collateral circulation by giving external support to the splanchnic circulation; but there is no doubt that too long delay of tapping is inadvisable. Some external abdominal compression should be used after paracentesis to prevent as far as possible rapid distention of the portal tributaries and reaccumulation of effusion. The operation should be performed as frequently as the reappearance of ascites, in considerable amount, requires."

Diuretics.—For discussion of the drugs, see Congestive Heart Failure. By general consent the best of them in cirrhosis are the mercurials, but the best is none too good. Christian (1936) felt that their use at times prolongs the intervals between tappings; Hayman (1936) also believed that this might be so.

Snell (1938) warned that if good increases in the volume of urine are not obtained, diuretics should be omitted, for he said their forced administration has often led to fatal hepatic and renal insufficiency. It is notable that Butt and Snell (1942) said that at the Clinic in recent years treatment devoted principally to the elimination of ascites by mercurial diuretics, restriction

of fluids and purgation, has been largely abandoned in favor of the type of dietetic approach described above.

Surgical Treatment.—A number of short-circuiting operations to divert blood from the collateral circulation, as well as measures to establish additional connections between the portal and the general circulations, have been employed with variable results. The best known of these, the Talma-Morison omentopexy, is believed by Höpfner to be beneficial in only one third of the cases, which is in agreement with the opinion of Eliot and Culp; Snell (1938) and Henrikson (1936) were no more sanguine. Cates (1943) reported that 42 per cent of the 38 patients operated upon in his series died within two weeks and that prognosis in the survivors seemed no more satisfactory than it would have been without resort to surgery; however, Greene (1943) seemed to be of the opinion that if the operation were not resorted to almost exclusively as a last resort but were done earlier in the disease in more cases the results might be more uniformly favorable. The operation is accompanied by high immediate mortality. Splenectomy, though giving great relief in some cases by removing a substantial burden from the portal circulation, is also accompanied by high surgical risk and not generally productive of so excellent results as in Banti's disease.

Hepatic Insufficiency.—In advanced cases in which there is a very great depression of liver function, such symptoms appear as loss of memory, delirium, convulsions and coma. These manifestations of toxemia may usually be made to disappear, at least temporarily, under the administration of adequate amounts of water and carbohydrate. It has now become the almost universal practice in these cases to administer 5 to 10 per cent dextrose solution intravenously either in amounts of 1 to 3 liters during the day or steadily by the continuous drip (venoclysis) method; Hendon (1930) gave as much as 500 Gm. of dextrose daily for five successive days by the latter method. The question of the advisability of employing insulin in addition seems to me to have been settled in the negative by Soskin and Hyman (1939), who pointed out that in a nondiabetic patient under these circumstances the administration of insulin promotes increased storage of glycogen in the muscles, thus causing the liver to pour out more sugar and therefore further diminish instead of replenish its supply of glycogen. Fagin and Thompson (1944) felt it probably wise not to employ morphine in advanced cases of hepatic insufficiency, since in 6 of their 15 patients dying in coma the development of stupor progressing to coma followed within a few hours the administration of morphine in usual dosage; it was their reasoning that probably in these cases the detoxification of morphine through its conjugation with glycuronic acid in the liver was interfered with.

CHRONIC GALLBLADDER DISEASE

Although chronic cholecystitis and cholelithiasis are possibly separate entities, they are nevertheless so similar in their symptoms and in the therapeutic measures with which we attempt to control them that it is legitimate and convenient to discuss the two conditions here under the common title of "chronic gallbladder disease." The victims of this disease are more often women than men and are usually near or past their fortieth year. "Female, fair, fat and forty" used to be a diagnostic alliteration of my student days

—but not a very accurate one, I am convinced, for many persons who are described by none of these terms do have the disease. The symptoms are those of dyspepsia, such as acid eructations, nausea, flatulence, heartburn, and especially chilliness and a feeling of weight in the abdomen after eating. During acute exacerbations there is pain and tenderness in the gallbladder region, chilliness, malaise, more or less precordial oppression and perhaps a slight bit of fever. There are usually frequent asymptomatic periods. A typical attack of gallstone colic—which is an acute condition not to be confused with the chronic state just described—occurs almost invariably in the middle of the night; the patient experiences excruciating pain in the upper right quadrant of the abdomen, which radiates all over the abdomen and into the back, the shoulders and even down the arms; she sweats profusely, is usually much excited and assumes many different positions, both in and out of bed, in an attempt to put an end to the agonizing pain. Such an attack usually persists only a few hours, but it may last for several days with remissions. When palpation becomes possible, on the subsidence of pain, it will be found that the gallbladder region is exquisitely tender; usually some degree of jaundice appears also after the paroxysm is over, or at least the urine will be bile-tinged and the feces undercolored. Chronic obstructive jaundice is rare in gallbladder disease unless there is an accompanying chronic cholangitis of considerable degree. It is to be noted that colic may occur in cases of chronic gallbladder disease in which there are no gallstones present; it is assumed that in these instances a motor type of dysfunction occurs to which the name "biliary dyskinesia" is applied. It is furthermore now well established (Rosenthal, 1944), that gallbladder disease and particularly gallstones are frequently encountered in the autopsies of elderly patients who did not have clinical histories diagnostic of cholecystitis or cholelithiasis.

Gallstones are supposed to be formed as the result of infection of the gallbladder, stasis of bile, or alteration in the chemical composition of the bile; as yet we have very little exact information on the subject. In chronic gallbladder disease, either with or without gallstones, the pathology in and about the gallbladder varies greatly; there may be a simple catarrhal inflammation with moderate swelling of the mucous membrane; or the viscus may be distended with mucopurulent material; or there may be many adhesions binding it in a distorted shape to the liver, pylorus and duodenum; or it may be much thickened and contracted and show actual erosions of the mucous membrane. Gallstone colic is due to spasm of the inflamed muscular viscus, to its distention with bile, to the temporary lodgment of a stone in the cystic, hepatic, or common duct, or to spasm of the sphincter of Oddi; but the cause of the much more vague constitutional symptoms of chronic, nonparoxysmal gallbladder disease is no more definitely known than is indicated in the statement that "the gallbladder becomes a focus of infection." Lyon believes that not only does the gallbladder become a distributing center for what he calls "poisoned bile," through its lymphatic connections with the liver and pancreas, but that hepatitis and cholangitis also play a prominent part in the pathologic picture; his position is that the liver, the gallbladder and the ducts are guilty of initiating a vicious circle since they pour into the duodenum "poisoned bile" which, being taken up by the mesenteric veins and lacteals, is conveyed throughout the body "to exert a harmful effect on all tissues." I do not believe that he has proved the "poisonous" nature of this bile, and do not see why one should not agree

with Carlson when he says: "Koch's postulates are still good science and good medicine. Has Lyon or Smithies reproduced the disease by putting the duodenal return into the duodenum of well persons or dogs?"

Gallstones were first recorded by Gentile da Foligno in the fourteenth century.

THERAPY

Dietetics, Nonsurgical Drainage and General Treatment.—It seems to me that about all there is to the *dietetics* of chronic gallbladder disease may be simply stated: (*a*) Nobody having ever conclusively shown in the human that substances high in cholesterol content (brains, sweetbreads, kidneys, liver, fish roe, egg yolk are the principal ones) are really conducive to gallstone formation, there is really no reason for eliminating these substances from the diet. (*b*) Fats make some of the patients uncomfortable probably by increasing cholecystokinin production and thus promoting gallbladder contraction, which may give rise to discomfort if the sphincter of Oddi does not at once become patulous. (*c*) If fats do not cause discomfort their employment may actually be of value in stimulating drainage in the above fashion. This is probably the chief service of olive oil, given usually in a 1-teaspoonful dose one-half hour before meals and before retiring.

Another method of promoting *drainage* is by the oral administration of magnesium sulfate, which, like olive oil, relaxes the sphincters. Hurst, in England, was well known as a stout champion of the use of the drug: the patient takes the largest dose short of that found upon experiment to cause looseness of the bowels—every morning the concentrated solution is drunk (it may be flavored with lactated pepsin or a small amount of the compound tincture of cardamom), and the patient then lies on his right side for a while before breakfast. Knight has been using the method in this country since 1922, and Soper since 1925, both reporting good results; the former also has some fat taken thirty minutes after the salt in order to contract the gallbladder. Lyon prefers to introduce the duodenal tube and, when its tip is in the correct location, to introduce 40 to 50 cc. of 33 per cent magnesium sulfate solution. In a little while, bile begins to flow out of the tube; at first it is light lemon-colored (A bile); then it changes to a more viscid consistency and is golden brown or green (B bile); and then it changes again and becomes much lighter and thinner than either of the two previous specimens (C bile). The A bile is said to come from the common bile duct, B from the gallbladder, and C from the liver itself (*i.e.*, freshly secreted bile) but there is very little proved fact to support these assumptions. Lyon cites many cases in which improvement in symptoms has followed upon single or repeated drainages with the duodenal tube, but study of his book and his subsequent publications leaves some of us rather skeptical. The enthusiasm of himself and his followers is at times almost hilarious, but they claim results in almost all the ailments to which man is heir, and they certainly do not show that the mental attitude of their patients is not tremendously affected by the atmosphere of almost religious awe with which the institution of a "drain" has come to be surrounded. Collins (1940) stressed the point, in behalf of tube drainage, that hypertonic magnesium sulfate solution given by mouth is reduced to isotonicity and that a part of the solution is converted in the duodenum into sodium sulfate which is thought perhaps to constrict instead of relax the sphincter of Oddi—however, by no means all of the magnesium sulfate is so converted and it is not proved that sufficient does not survive

to promote the "drainage" even though the ritual of the tube has not been performed. As to the possibly harmful effects of having infected bile pass out through the intestine instead of through the tube, witness Carlson: "We are swallowing bacteria every day. There are a few bacteria that are specifically toxic in the intestine. There are a few toxins poisonous by mouth, but, so far as I know, we could eat pus, ordinary pus, and not be influenced, excepting esthetically. It is not clear, therefore, that finding bacteria or pus in the duodenal content means injurious effects from the bacteria or bile lower down." It seems to me that the only significant difference between the peroral and the tube methods of "nonsurgical biliary tract drainage" is that in one the bile goes down and in the other it comes up; in either case it goes out. The Lyon type of tube drainage is being performed less and less as a therapeutic measure as the years go by.

Bile salts, perhaps best given in the form of decholin, 4 to 8 grains (0.25 to 0.5 Gm.) two or three times daily, stimulate the production of bile; but since no one has proved that in gallbladder disease the liver usually fails to secrete properly, I cannot understand the rationale of the routine employment of bile salts. Ivy and Berman (1939) seemed to look upon the two chief indications as: (*a*) to "flush" the biliary passages with a copious flow of bile of low viscosity in the hope of counteracting a tendency toward stasis; (*b*) instances in which there is sufficient hepatitis to diminish bile salt synthesis but not to prevent bile pigment excretion, *i.e.*, bile salt deficiency in the presence of pigmented feces. The evidence for the very frequent occurrence of either of these indications is not clear to me in the literature. However, bile salts are very plentifully employed in practice; therefore I must be wrong.

Methenamine (*urotropin*) is *not* a biliary antiseptic; Burnham long ago laid that ghost, nor did Tsu's (1937) reinvestigation supply it with any new stalking power, so far as I am able to judge.

Spa treatment is often of value in cases of chronic gallbladder disease, not so much because of the mineral content of the waters as because of the fact that a large quantity of water *per se* is drunk, and also by reason of the really tremendous psychic readjustment which takes place in many people when they visit a pleasant health resort.

Gallstone Colic.—In a very mild attack, a simple enema of warm physiologic saline, or of 1 per cent sodium bicarbonate, will often bring relief; a dose or two of a carminative (for prescription see Index) nicely supplements this treatment. Hot fomentations, as described under Pneumonia, should be applied to the gallbladder region. In a severe attack, none of these measures is of any avail; morphine, or dilaudid, will usually bring relief. Some men prefer pantopon in dosage of $\frac{1}{3}$ to $\frac{1}{2}$ grain (0.02–0.03 Gm.) by mouth or hypodermically. Betterman (1943) has employed the new synthetic analgesic drug, demerol, with satisfaction in biliary colic; the drug, which has been shown to be addictive like the opiates, is usually employed in a dose of $\frac{5}{8}$ to $1\frac{1}{2}$ grains (50–100 mg.). It is customary to employ atropine with the opiates, but Walters *et al.* (1937) did not find that this drug even in large dosage was able to overcome the contraction of the sphincter of Oddi caused by morphine. In a small series of cases, Bauer *et al.* (1931), at the Massachusetts General Hospital, caused prompt relief by slowly injecting intravenously 20 cc. of a sterile 5 per cent solution of calcium chloride; I understand that the metodh is still in use and productive of good results provided there is

not too much associated inflammatory disease at the time of the attack. Beware, proceed calmly here, even though the patient is writhing in pain; see Lead Poisoning for the reasons. In a small series of cases, McGowan *et al.* (1936) obtained relief through the use of nitrites as in angina pectoris; Walters *et al.* (1937), Best and Hicken (1938), Volini and O'Brien, (1939) and McGowan and Henderson (1940) also reported satisfaction with these drugs in small series of cases in which sphincter spasm appeared to be the cause of the pain. Gladstone and Goodman (1944) injected 0.25 to 0.5 Gm. of aminophylline (theophylline ethylenediamine) and obtained satisfactory relief of pain in their small series of cases; the drug was given intravenously and with no bad effects but the authors warned that the injection must be made very slowly. In rare cases, light or even relatively deep general anesthesia must be instituted in order to bring release from the agony. Return to full diet after the attacks must be very gradual.

Surgery.—Medical measures, though they will carry a patient through an attack of colic, will not cure gallstones, that is to say, we know of nothing that will effect the dissolution of the stones, and so long as they remain these attacks are likely to recur in those subject to them. There does not seem to be general agreement among surgeons as to the advisability of operating during the attack; at least the emergency is not considered at all comparable to that of acute appendicitis, and perhaps most surgeons think that delay of several days is of advantage in allowing time in which to improve the patient's general condition. Bearse (1944), reviewing the matter in the light of the shortage of hospital beds in War II, concluded that operations may be safely deferred in patients with gallstones so long as there is no evidence of complications and provided postponement is not so protracted that it may impair the patient's resistance to the operative procedure. Indeed, many medical men feel there is no evidence that delay occasions any serious threat to the welfare of the patient whose colic has been mild, and that recurrence may not take place for a very long time. However, when a stone has become impacted in the common duct, or when the attacks are frequent and the general health failing, the consensus is that operation is certainly indicated. Alvarez (1944) says he recommends immediate operation also to those persons with a bad gallbladder who have to travel much or live in out-of-the-way places where a good surgeon is not available. Common duct operations are the most dangerous—a fact upon which many surgeons base their plea for operation in any case in which gallstones have been diagnosed with certainty, since this will in most instances save the patient the risk of a possible operation for stone impacted in the duct. Miller's (1932) study of the association of cardiac pain with disease of the gallbladder has caused a number of surgeons to recall instances in which "heart trouble" disappeared after cholecystectomy.

The problem of the persistence of "biliary dyskinesia" after operation for presumed cholecystic disease is well known to all and most perplexing to the surgeons. Recently, Gray and Sharpe (1944) of the Mayo Clinic said that in cases in which pain persists or recurs after cholecystectomy, and in which reoperation is deemed necessary, diligent search should be made for a suspected remnant of the cystic duct, whether or not calculi are suspected in the common bile duct; they also laid great stress upon the importance of operating in the first place only on those patients who present definite and conclusive clinical and roentgenographic or both types of evidence of disease in the biliary tract.

DISEASES OF THE RESPIRATORY TRACT

CHRONIC BRONCHITIS AND EMPHYSEMA

Sydenstricker, of the United States Public Health Service, has pointed out that the use of death rates as an index of the prevalence of disease has become so universal that the problems and aims of public health are set forth almost entirely in lethal terms when statistics are used. Valuable statistics these, but their use unfortunately sometimes serves to obscure the fact that there is still a tremendous amount of "ill health" in the world, even though people so fortunate as to dwell in civilized lands do not die so young as they did a few decades ago. What doctor of any experience at all needs to be told that the ailments of most individuals are seldom dangerously severe, though they are nevertheless of very great importance both to the individual and the community? Among these important affections that make people simply "sick," acute and chronic bronchitis and emphysema and frank bronchiectasis (implying, as I intend, that many cases of "chronic bronchitis" are really unrecognized bronchiectasis) hold a prominent place; indeed, together with the common cold in its various stages, they occupy the *most* important place, for it is certain that an upper respiratory infection is the diagnosis most often made in home visits in Great Britain and the United States—doubtless this is also the case in the other North Temperate countries as well. The winter cough, often becoming a year-round cough, of late middle-aged and elderly people, coupled with shortness of breath and cyanosis on exertion, *i.e.*, that which we call chronic bronchitis and emphysema, *may* be just that, but the wise practitioner makes a careful search for a possible underlying cardiovascular disease, aortic aneurysm, bronchiectasis, asthma, gout, syphilis, or some other debilitating disease.

THERAPY

The treatment of chronic bronchitis and emphysema has advanced hardly at all since the days of our great-great-grandfathers. Moderation in all things, a quiet and regular life with shunning of all vigorous pursuits, a residence in the South during the winter—all of these measures are quite helpful to the few for whom they are possible. It would seem that the sojourn in the South had best not be in a region of excessive dampness; Cohen (1944) found many cases of chronic bronchitis much exaggerated in individuals who had come to Panama and he ascribed this chiefly to the dampness of that region. The treatment of cough is described under Common Cold. Both Wilson and Findley (1944) and Christie (1944) said that ephedrine will bring relief to a considerable number of these patients; the former authors offered the following prescription in which the effects of ephedrine are obtained together with the relaxing action of belladonna and the expectorant action of the iodide:

℞	Ephedrine sulfate	gr. xv	1.0
	Tincture of belladonna	ʒi	30.0
	Potassium iodide	ʒi	30.0
	Syrup of cherry	ʒiv	120.0
	Water to make	℥viij	240.0

Label: Teaspoonful every 4 hours.

Some patients are relieved by the performance of exercises designed to improve the expiration, while others are helped by the abdominal belt as described in Bronchiectasis. Inhalation of oxygen or oxygen and helium mixtures sometimes temporarily relieves the difficulty in respiration but of course these agents are seldom available to this type of patient who is not in hospital.

BRONCHIECTASIS

Increasingly in recent years the profession has become aware of the large number of cases of bronchiectasis which occur independently of any association with pulmonary tuberculosis, pneumoconiosis, or tumor of the lung; indeed, one finds some qualified observers who feel that the condition is about as common as tuberculosis. Case distribution is about equal at all ages, according to Chapman and Anderson (1938), but most cases seem to begin in the first and second decades with the onset rate diminishing rapidly into old age. The patient with this type of bronchial dilatation is more or less chronically ill in appearance, is dyspneic on exertion, has clubbed fingers, has fever at intervals, coughs a great deal and usually but not invariably expectorates a great deal; the sputum is often but not always very foul, and often but not always it stratifies into three layers on standing. Pulmonary hemorrhages are of frequent occurrence. It is generally considered that the classification of the dilatations into the cylindrical, saccular and varicose (beaded) forms comprises the vast majority of cases; other classifications, such as that of Chapman and McCullough (1941), are far too complex for presentation here. It seems that bronchiectasis may involve part of one lobe, the whole of one lobe, or part or all of many lobes; but apparently after it is once established it seldom spreads from one lobe to another. But infection may spread from the bronchial walls to involve the peribronchial and pulmonary tissues, giving rise to suppuration and foul sputum. With regard to etiology the consensus is that the condition is a sequel of pulmonary infections such as pneumonia, empyema, abscess, tracheo-bronchitis, or influenza, or of chronic sinus disease; Rilance and Gerstl (1943) felt that bronchiectasis secondary to tuberculosis is in most instances merely a benign bronchial dilatation not associated with abnormality of bronchial function. Olsen (1943), studying the material at the Mayo Clinic, said that the indications are that both congenital and acquired components enter into the production of most instances of the disease. Watson and Kibler (1938) believe that there is a definite chain of events in most cases: first, an allergic bronchitis; second, atelectasis; and finally, bronchiectasis. The only extensive prognostic study I have seen in which no case that had not been followed for at least five years was included is that of Bradshaw *et al.* (1941): 34.5 per cent of their 171 patients died of bronchiectasis or its complications, the average duration of life in the dead patients from the onset of symptoms being 13.5 years. But this is a serious disease not only because of its high, if long postponed, mortality, but also because by its very nature it handicaps its victim psychically, socially and economically, as well as physically. Saphir (1943) pointed out that there is a type of myocarditis that occurs in patients with bronchiectasis, and Campbell and Moersch (1942) pointed out that the patient who has even minimum bronchiectasis constitutes an

increased risk, so that when surgical operation is indicated for such a patient additional attention should be given to this pulmonary condition. The differential diagnosis is often very difficult and usually rests finally upon the injection of iodized oil into the bronchial tree with subsequent roentgen study.

THERAPY

General Medical Treatment.—The general hygienic treatment of tuberculosis is profitably employed in advanced cases of bronchiectasis; *i.e.*, the patient should rest a great deal, if not entirely confined to bed, and should be given a well-balanced nutritious diet and as much spiritual encouragement as possible.

Postural Drainage.—Patients do not have to be encouraged to employ this measure for they have often found the most suitable posture for drainage of their own accord. King (1939) said that with lower lobe involvement the best position is on the face with the shoulders lower than the hips; some patients lie across the bed with the shoulders near the floor, others kneel in a chair with the hands on the floor. Alexander (1944) remarked that the taking of a half dozen deep breaths before each half dozen hard coughs loosens the secretions better for expectoration and aerates the affected portion of the lung better than if the inversion and coughing are alone relied upon. Lying on the back with the foot of the bed moderately elevated seems to serve best in cases with the right middle lobe or lingula of the left upper lobe involved; in the rare upper lobe cases the sitting posture is said to be the most satisfactory, and if the disease is in the lower part of the upper lobe the position of choice is lying on the uninfected side. In some hospitals postural drainage beds are available nowadays.

Lipiodol Injections.—The oil is introduced either through the bronchoscope or by injection from a syringe, or it is inhaled from the mouth. All of these are special technics which of course cannot be learned from the pages of a book. Opinion varies as to the action of the oil: some say it dilutes the sputum and allows it to be raised with greater ease, others that it displaces the sputum from the bronchiectatic cavities, and others that it merely reduces irritation by coating the bronchial walls. Some patients are helped, others are not; it does not seem possible to discover in the literature what the proportions are.

Bronchoscopic Drainage.—Sometimes this procedure is resorted to. King (1939) said that patients are often aided enough to insist on continuation of the treatments, and Diamond and Van Loon (1942) referred to the dramatic subsidence of symptoms which often follows bronchoscopic removal of copious or viscid exudate. Alexander (1944) said that satisfactory improvement occurs in most patients but that a relapse in several weeks or months usually calls for repetition of the bronchoscopic treatment.

Collapse Therapy.—It is the consensus that these measures, so useful in pulmonary tuberculosis, are seldom helpful in bronchiectasis and that their employment may preclude subsequent lobectomy.

Abdominal Belt.—Alexander and Kountz (1934), Gordon (1934), and Meakins and Christie (1934) each described a special type of abdominal binder the wearing of which was said often to give relief; some patients, however, cannot tolerate these belts even though they give them partial respiratory relief.

X-Ray Therapy.—Berck and Harris (1937), at Mount Sinai Hospital in New York, treated a small group of chronic cases with moderately large doses

of roentgen ray with a considerable degree of improvement in a fair proportion of the cases. Fink (1941) said that they concluded at the University of Minnesota Hospitals that little was gained by roentgen therapy usually, though it might be worth trying in selected cases.

Drugs.—Of course the sulfonamides have been tried but one does not hear that the results have been brilliant; likewise, the study of Stookey *et al.* (1945) indicated that not a great deal is to be expected from penicillin. It seems that neoarsphenamine may be of value in occasional instances, particularly if fusospirochetal organisms are present and the sputum is foul; both King (1939) and Singer (1939) mentioned the drug. Creosote is also used to overcome the foul odor, in some such prescription as the following:

℞	Creosote (beechwood)	gtt. vj	0.4
	Glycerin	℥j	32.0
	Peppermint water (or plain water) to make	℥iij	96.0
	Label: Two teaspoonfuls every two to four hours, well diluted.		

This prescription contains a small amount of the drug, but when it is finished the next should contain double this quantity—*i.e.*, 12 drops. The creosote should then gradually be increased to the point of tolerance as marked by anorexia or other gastro-intestinal disturbances. The dose is then reduced to the amount the patient well tolerates and is best given directly after meals. When the larger doses are being given the urine should be frequently examined for albumin, or for signs of phenol poisoning, and if the kidneys are at all disturbed the creosote should be stopped at once. Creosote carbonate is sometimes substituted for creosote in doses twice or thrice the size. Creosote is sometimes vaporized by igniting it and the patient, breathing the fumes. in a closed room, coughs violently and expectorates profusely; King quoted authors who have found these "baths" useful when given two or three times daily.

Climate.—Climatic change sometimes benefits the patient, and it is not always the warm dry climate which is best, for some individuals do well at the seashore or in the mountains.

Desensitization.—Watson and Kibler (1938) reported considerable improvement in some of their cases in which desensitization therapy was employed; most common sensitizations were to feathers, pollens, orris root, house dust and wool, but there were a few cases in which foods were said to have been the most important factor.

Lobectomy.—The technic of this operation has improved so much that many thoracic surgeons are now hopeful of some day being able to offer complete relief in this way to the majority of patients. It is considered that in skilled hands in properly selected cases the mortality should be very low. Clagett (1942) made a plea for operation on the patients as young and as early as possible; Diamond and Van Loon (1942) in taking the same position pointed out that as a rule children tolerate lobectomy better than adults and that in them there is a far better compensation for the loss of the excised areas.

ABSCESS OF THE LUNG

Abscess of the lung may follow a severe bruise of the chest wall or a penetrating wound of the lung, or it may occur during the course of chronic pulmonary tuberculosis, or it may occur as a sequela of pneumonia, especially

the influenzal type of pneumonia. Its occurrence following operations in the mouth and throat of adults is notorious, particularly when general anesthesia has been employed. Whatever the cause, the cardinal symptoms and signs are: cough and explosive expectoration, localized chest pain, foul breath and sputum, elastic tissue in the sputum, dullness on percussion over a circumscribed area and positive x-ray findings. Sometimes the symptoms of sepsis, such as intermittent fever, sweats, high leukocytosis, etc., are present. However, diagnosis is by no means always easy and not infrequently is made only at the autopsy table.

THERAPY

The so-called conservative therapy of lung abscess is about the same as that of bronchiectasis, *i.e.*, general building-up treatment, postural drainage, bronchoscopic drainage, arsenicals or the new sulfonamides, and a miscellany of other drugs, measures and procedures. Its record has not been good though one should note that Blake and Craige's (1943) trial of penicillin in three cases gave results which they thought sufficiently satisfactory to warrant further trial in other cases. The essence of this type of treatment, if I understand it, has been to try everything possible in order to avoid surgery because an even larger number of patients succumb to surgical than to the above listed medical measures. Now, however, the surgeons are showing that this "conservative" attitude has been all wrong, for Neuhof and Touroff (1940), and Overholt and Rumel (1941), by treating lung abscess as a surgical problem from the onset and instituting immediate and early drainage were able to show results never before attained. Overholt and Rumel, for example, showed that external drainage of complicated lung abscess has an operative mortality of 32 per cent and a cure rate of only 26 per cent, while external drainage of simple lung abscess has an operative mortality of 6 per cent with a cure rate of 94 per cent; more recently Brantigan and Looper (1944) said of the latter "the mortality will be under 10 per cent." Since most simple lung abscesses are of short duration and most complicated lung abscesses are of longer duration, it becomes obvious that lung abscess is best considered as primarily a surgical condition in which early operation is indicated.

PLEURISY

Pleurisy, which is usually abrupt in onset, sometimes with pronounced chill, often follows exposure to cold, or it may be a sequela of some other respiratory affection; in a few cases neither antecedent condition appears in the history. There is a stabbing pain in the side, which is aggravated by breathing and changes in posture; usually a hacking cough, which also aggravates the pain; increased respiration, several degrees of fever, leukocytosis; and a number of typical physical signs, the chief of which is a leathery friction rub. In some cases the pain is referred to the abdominal region, which makes differential diagnosis somewhat difficult; also, in some instances, the patient never at any time experiences any pain. Latterly an interesting theory has arisen which explains the pain in pleurisy as due not to friction of the opposing inflamed parietal and visceral membranes, as is the time-honored belief, but solely to tension of the inflamed parietal layer which is stretched during respiration.

Pleurisy with effusion differs very little in its onset from the dry variety, but when the inflamed pleural surfaces begin to be separated by the fluid, the pain disappears and dyspnea develops; it is not in order in this book to describe the numerous other physical diagnostic signs of effusion. Occasionally a patient feels very little subjective distress whatever.

The immediate prognosis in both forms of pleurisy is good. A dry case usually clears up gradually in two to three weeks; a case with effusion is often protracted much beyond this period. However, the fact that an attack of pleurisy is looked upon as presumptive evidence that the individual who suffers it is tuberculous makes the disease of much more serious import. Some physicians of vast experience maintain that *all* cases of pleurisy are tuberculous; others hold that all cases not accompanied by the signs of a known infection, such as typhoid, are tuberculous; others are doubtful regarding dry cases (only 4 of Fulton and Hahn's, 1931, 40 cases developed pulmonary tuberculosis during an average period of observation of seven years) but believe all cases with effusion to be of tuberculous origin (Trudeau, 1939, found x-ray evidence of the disease in 29 of 83 cases; 25 per cent of the white and 56 per cent of the Negro and Indian patients in Farber's, 1943, series of 111 cases followed for three to thirteen years later developed tuberculosis); while there are those who, lacking positive evidence of tuberculosis in a first attack, always make a diagnosis of tuberculosis in any patient who has pleurisy twice, whether with or without effusion.

Boerhaave (1668–1738) was the first to show that pleurisy is an affection of the pleura alone.

THERAPY

The patient with dry pleurisy should be kept at rest—indeed he will impose the most absolute immobility upon himself, usually lying on the affected side with the shoulder depressed and the arm stretched along the body. Compresses are hardly worth using for relief of the pain. The best measure is the application of adhesive plaster strips (2-inch width) with the chest in the expiratory position. They should pass from the vertebral column to the midline in front, at right angles to the column, not slanting with the ribs; begin below and let each strip slightly overlap its predecessor. The cough does not usually require special treatment if the affected side is immobilized in this way. In severe cases, 1 grain (0.065 Gm.) of codeine sulfate, or if necessary $\frac{1}{4}$ grain (0.015 Gm.) of morphine sulfate or $\frac{1}{32}$ grain (0.002 Gm.) of dilaudid hydrochloride, should not be withheld in the beginning. A number of physicians believe that calcium and parathyroid extract are effective at times in preventing effusion or promoting its resorption; for methods of administering these drugs, see Lead Poisoning.

Shaw (1935) pointed out the danger of inducing basal atelectasis, especially in elderly individuals, through partial immobilization by strapping or as a result of respiratory depression consequent upon the use of opiates. In two instances in which atelectatic pneumonia had already developed, he induced shallow pneumothorax with 200 to 250 cc. of air, and obtained almost immediate relief and the recovery of both patients, in whom it had been felt that the prognosis was extremely grave at the time of making the injections. He believed that the usual objections to artificial pneumothorax—risk of secondary pleural infection, of causing or increasing myocardial distress, of pleural shock and air embolism—are bogies with a very infrequent incidence.

When fluid appears in sufficient quantities to aggravate the condition of the patient it should be removed by paracentesis. The indications for, and and the technic of, this procedure are to be learned in an apprenticeship upon the wards and not from the pages of a book. Attempt should not be made to remove the effusion by diuresis or catharsis, for the fluid cannot return with sufficient rapidity through the inflamed serous membrane to make up for the loss of water by way of the kidney or bowel; the patient will thus only be weakened to no purpose. Blisters are also of little or no value.

The necessity for looking upon an individual who has once had an attack of pleurisy as a tuberculosis suspect is of the utmost importance, since by accepting such an attack as a sign from the gods that a readjustment of the mode of life is in order, we may sometimes entirely prevent the appearance of a frank pulmonary tuberculosis.

Trudeau (1939) found the prognosis excellent in cases with effusion, whether they have negative, doubtful, or extremely slight apical pulmonary findings by x-ray—if these patients receive at least four months of sanatorium care.

LARYNGITIS

Acute laryngitis appears rather suddenly with a dryness and tickling in the throat and some pain on swallowing; oftentimes there is tenderness to pressure made upon the protruding portions of the voice box in the neck. The voice becomes husky and speaking is not only painful but is also provocative of extreme weariness. Cough may not be present in the beginning but it usually develops quite soon and serves to eliminate considerable amounts of mucus. Not infrequently the voice is completely lost during the few days' duration of the attack.

Laryngitis usually follows exposure to sudden changes of temperature, sudden climatic changes, inhalation of irritating materials, or excessive or faulty use of the voice. Occasionally the condition becomes chronic; in these cases there is nearly always a discoverable source of chronic infection in the nasopharynx.

THERAPY

Rest of the body, and especially rest of the voice, are the most important elements of treatment. Complete silence for forty-eight hours works wonders in these cases, but is practically never possible of enforcement.

Confinement to a room in which the temperature is maintained at an even level and the air moist is helpful. Some patients like to apply cold compresses to the throat. The use of a steamy inhalation mixture, such as is described under the treatment of Common Cold, is soothing. Gleason said that the taking of 10 drops of dilute nitric acid, in a glass of water every two hours, is often helpful in the aphonia of singers and speakers, a statement which is fully corroborated by the experience of many of the older practitioners.

The use of drugs to control the cough is doubtfully advisable since it serves a benign purpose; when it becomes too severe, however, the preparations described under the treatment of Common Cold should be considered.

Oftentimes reeducation in the use of the voice is necessary for those who are suddenly thrust into a public-speaking career.

NEPHRITIS AND NEPHROSIS

Acute diffuse glomerular nephritis usually makes its appearance, abruptly or insiduously, in children or young adults several days or weeks after apparent recovery from an upper respiratory infection or from one of the acute streptococcic infections, such as tonsillitis, scarlet fever, rheumatic fever, or erysipelas. Many observers now believe that the attack is the expression in the kidney of a widely diffused vascular inflammation, which may be allergic in nature. Cases occurring during a subacute bacterial endocarditis are usually looked upon as "focal" rather than "diffuse," the differentiation being made on the smaller number of glomeruli found to have been involved in the rare specimens that come to autopsy, plus the absence of hypertension and edema. In the common or diffuse form there are present both edema and hypertension, but the former is rarely of the marked pitting sort seen in nephrosis, and the hypertension is usually not inordinately high and very rarely may not be present at all. There is more or less albumin in the urine but the characteristic feature of these cases, in addition to the hypertension, is the presence of red blood cells and red cell casts often enough to cause the urine, which is diminished in amount, to have a smoky brown color.

Ordinarily the acute death rate may be reckoned at 5 to 10 or 12 per cent. The prognosis as regards ultimate recovery without permanent sequelae, though now admitted to be better than formerly believed, varies considerably. Cass (1939), studying 88 cases in England, found that the condition ultimately became a chronic one in 32.0 per cent of those who had not died in the acute attack; Snoke's (1939) figure for a large series of cases in San Francisco was 47.2 per cent, while for a series in Rochester, N. Y., it was 13.7 per cent; here in Milwaukee, Murphy and Peters (1942) reported the following outcome in 205 cases studied during a ten-year period: 12.6 per cent died during the acute stage; 17.0 per cent were discharged recovered but were not reexamined; 34.1 per cent recovered and were found healed upon reexamination; 9.2 per cent were found latent upon reexamination; 26.8 per cent became chronic nephritics. Most clinicians are now in agreement that patients who experience the most turbulent onset often have the best outlook for complete recovery. Cases advancing toward chronicity frequently develop subacute exacerbations during which there is some elevation of temperature and the urine is clouded with blood and casts, but as the glomeruli are gradually destroyed during months and years the urine contains less blood and fewer erythrocytic casts, and finally nitrogen retention, manifested by rise in blood urea and creatinine, makes its appearance foretelling uremic termination—though it has been remarked that in all *fatal* cases of chronic nephritis characterized by severe nitrogen retention there is an acidosis severe enough in itself to be the actual cause of death. It has also come to be increasingly recognized in recent years that severe anemia is an accompaniment of decreasing renal efficiency, though it may also appear early in the acute cases. Marchand and Finch (1944) reported fatal spontaneous potassium intoxication occurring in 2 cases of uremia with renal failure and oliguria, and Dickes (1942), and Roen (1944), published studies indicating an interesting relationship between the blood phenol level and the outcome in uremia; con-

siderable disturbances in calcium metabolism are also sometimes seen. Lipemia, often very marked, tends to decrease in the terminal stages of the disease and the plasma lipid content may fall below normal just before death.

The striking characteristics of *tubular* (*degenerative*) *nephritis* which distinguish it in its *pure* form from the glomerular type, are hyaline, waxy and fatty casts but no blood or blood casts in the urine, marked and persistent edema, and albuminuria without hypertension or nitrogen retention. This type may also appear acutely in children in the course of streptococcal or other blood stream invasions, or as a mild form complicating Asiatic cholera, diphtheria, malaria, syphilis, typhus, yellow fever and possibly other infectious diseases. It is the nephritis sometimes caused by mercury and the arsenicals, also the nephritis seen in the late toxemia of pregnancy. If, in addition, there is observed an increased blood cholesterol, refractile globular bodies in the urine, a low metabolic rate, low serum protein with a marked disturbance in the ratio of serum albumin to serum globulin, and a tendency toward a protracted course with relatively frequent complete recoveries or death from intercurrent infection without the appearance of signs of severe inflammatory renal disturbance—in these cases the diagnosis of *lipoid nephrosis* is made, which is considered by some observers to be a rare entity not directly related to inflammatory nephritis.

The type of kidney disease known as *arteriolosclerotic nephritis* is only one element in the cardiovascular-renal syndrome, which begins with "essential" hypertension, progresses to arteriolar disease of the body as a whole and not solely of the kidneys, and ends often in cardiac or apoplectic death before kidney complications of a serious nature have appeared. The urine is much increased in amount and low in specific gravity and contains often only a small amount of albumin and a few hyaline casts. Edema is not a usual feature of the pure form, but ultimately uremia appears in association with the slowly increasing nitrogen retention. More rapidly progressive cases are designated "malignant."

So far as is yet known, the first description of kidney disease was that of Aetius (500 A.D.), who is said to have found at autopsy that certain cases of dropsy were associated with hardening of the kidneys. Rhazes (860–932 A.D.), the great Arabian clinician, probably also recognized the entity but no further advance toward its understanding was made until Avicenna, that "convivial Omarian spirit" at the court of Bagdad, noted that in dropsy the urine was considerably altered. Then Saliceto, in the middle of the thirteenth century, provided the classical description of edema associated with contracted kidney, and Malpighi (1628–1694), aided by the great discoveries of Harvey (1578–1657), established the function of the capillaries. Thus were laid the foundations upon which Richard Bright (1789–1858) was able to erect his anatomico-pathologico-clinical classification a hundred years ago.

THERAPY OF ACUTE NEPHRITIS

Rest.—It is the consensus of course that the patient should be in bed and at complete rest during the early stages, but there is difference of opinion regarding how long this absolute rest should be imposed. Page (1940), it seems to me, has been for keeping the patient in bed as long as this may be easily done, but Goldring (1941) believed that he should be allowed out of bed when the hypertension and edema have disappeared even if there are still urinary abnormalities, for he made the point that albumin and some

blood may persist in the urine for three to six months longer even in those who ultimately recover. Murphy and Rastetter (1938) felt that the persistence of hypertension and urinary and other laboratory findings after three months mark the transition into chronicity and that nothing is gained in keeping the patient in bed any longer.

Diet and Fluids.—There has been argument in the profession since time out of mind regarding the type of diet to be employed in acute glomerular nephritis, with a good deal of wobbling in more recent times as bits of experimental evidence from small animal observation have been introduced to bolster one side or the other. As a matter of fact if anyone has yet proved the harmfulness of allowing the patient as much of a mixed diet, including proteins, as he wants to take (which is usually not much in the beginning), I can only say that I have not seen the report. Fluids, too, may be given in such quantities as the patient desires. Obviously, sodium chloride should be restricted in the presence of edema. Excessive acidity of the urine may be corrected by the use of fruit juices or perhaps 15 grains (1.0 Gm.) of potassium citrate. Certainly enough time has passed for the "hunger-thirst" cure of Volhard to have justified itself unequivocably but it has failed to do so. Murphy and Pietraszewski (1940), here in Milwaukee, compared high-protein and relatively low-protein diets and found that the patients did as well on the one as the other but were more satisfied on the high-protein diet; incidentally, the high-protein was an acid-ash diet and the other an alkaline-ash diet, so this study provided a comparison of these factors also. Goldring (1941) has said that it is the practice at Bellevue Hospital to allow the patients to take the regular ward diet, only restricting sodium, and that the statistical results are as good as those obtained under strict regimens. During any extended period when the patient is not taking a full diet supplementary vitamins should be given.

Edema.—It is impossible in the present state of our knowledge to direct any measures toward the relief of the edema of acute glomerular nephritis since it is due to increased capillary permeability resulting from bacterial toxin injury. Diuretics are not indicated but salt restriction is of course advisable since the more sodium in the tissues the more water they can hold. The edema of acute tubular (degenerative) nephritis, with reduction in plasma proteins, requires to be handled in principle as the edema of chronic nephritis (see below).

Nonuremic Convulsions.—This type of convulsion, of rather frequent occurrence in children, is characterized by the premonitory symptoms of sudden violent headache and visual disturbances, central vomiting, and a rapid rise in blood pressure, and is often followed by coma, a Kernig and a Babinski sign and occasionally transient paralytic symptoms. The syndrome, not being due to the retention of nitrogenous products and hence not being true uremia, is considered to result from cerebral edema and angiospasm; it is definitely relievable by depleting measures. Magnesium sulfate is given in large doses—1 to 2 ounces (30–60 cc.) of a 50 per cent solution by mouth every four hours. If this method of administration does not check the cerebral symptoms and reduce the blood pressure the drug is injected intramuscularly. Usually 0.2, occasionally 0.4 cc., of a 25 per cent solution per kilogram (2.2 pounds) of body weight is the dose; the effects are usually seen in fifteen to thirty minutes, but failing, the injection can be relatively safely repeated after two or three hours. Blackfan abandoned the intravenous route after

finding the intramuscular just as satisfactory, but Plotz *et al.* (1937), confirming Blackfan's favorable use of the drug, used it by either route; intravenously the same dosage may be employed as is used intramuscularly; Goldring (1941) also used it intravenously. Alarming toxic symptoms rarely follow the use of magnesium sulfate parenterally, but it is well to be prepared to combat respiratory depression by the slow intravenous injection of a few cubic centimeters of 25 per cent calcium chloride solution. Hypertonic dextrose may be given intravenously instead of magnesium sulfate; 25 to 100 cc. of 50 per cent solution are most often used. An objectionable feature of this use of dextrose is that it frequently induces a high secondary rise in cerebrospinal fluid pressure. Both Page (1940) and Lueth (1941) have spoken favorably of the intravenous administration of 50 per cent sucrose solution, giving from 50 to 250 cc. but injecting very slowly if cardiac failure is impending. In rare instances sucrose seems capable of causing tubular degeneration, but the effect is only transient and it would seem from the work of Lindberg *et al.* (1939) is not likely to alter renal function. Venesection may be of value; spinal puncture is definitely of aid if coma supervenes—but Goldring warned that the fluid must not be permitted to run out fast.

Hypertension.—In most instances the hypertension *per se* is transient and does not call for treatment directed specifically toward its relief, which is fortunate since we know so little of its causation. In some instances magnesium sulfate parenterally, as in treatment of convulsions (see above), relieves hypertension; Rubin and Rapoport (1941) felt that probably the effect is due to a relaxation of the generalized vasospasm through local action on the smooth muscles of the blood vessels.

Heart Failure.—It is the general impression that myocardial involvement is rare in acute glomerular nephritis, but Whitehill *et al.* (1939) found the signs of circulatory insufficiency very frequently in the moderately severe and usually in the very severe cases among their 138 patients. La Due's (1944) study indicated the possible importance of hypertension in the pathogenesis of this type of congestive failure, while Odel and Tinney (1943) pointed out that patients who die during the acute phase of glomerulonephritis may die from heart failure. This type of congestive heart failure responds to digitalis or ouabain in the usual way (see Index for methods); Goldring (1941) felt that the drastic treatment (ouabain intravenously) is usually called for.

Anuria.—Anuria is not a common occurrence, which is fortunate for it is usually accompanied by uremia and is likely to be fatal. Page's (1940) recommendations for treatment may be outlined as follows: (*a*) Catheterize to be sure there is no obstruction. (*b*) Give 50 per cent dextrose intravenously. (*c*) Try a hot bath lasting thirty minutes or more, simultaneously administering 400 to 500 cc. of fruit juice. (*d*) If there is acidosis, give sodium bicarbonate by vein. (*e*) If all these measures fail and little or no urine has been passed for three days, decapsulation of the kidney should be tried. Murphy (1936) has increased the fluid intake to 2000 or even 3000 cc. per day, regardless of the presence of edema or the danger of inducing it. Goldring (1941) expressed skepticism of the value of any efforts to get the urine flowing again, pointing out particularly that if the cause of anuria is a deficient blood flow through the glomeruli, as it probably is, it is difficult to see how the administration of hypertonic solutions of sucrose or dextrose would correct the functional disturbance. It is significant, too, that decapsulation is performed much less frequently now than a decade or two ago.

Uremia.—See under the same heading in the therapy of Terminal Nephritis. In acute glomerular nephritis the symptoms are often alarming but the condition is apparently not of serious moment since as many complete recoveries seem to occur in those who develop an extremely high nonprotein nitrogen as in those who do not.

Treatment of Infections.—Williams, Longcope, and Janeway (1942) used sulfanilamide in 42 patients in the acute stage of nephritis, nearly all of them being patients from whom beta hemolytic streptococci had been cultured from some focus. The results indicated that under the drug the foci of infection cleared up more rapidly, the signs of renal damage disappeared more rapidly, exacerbations of the nephritis following tonsillectomy occurred less frequently, the duration of edema and hypertension was reduced, and the proportion of clinical recoveries was greater (74.3 per cent in the 39 patients followed for at least two years). Murphy and Wood (1943) found sulfonamides distinctly beneficial in the three cases in which they were used. It will be of great interest to see if such results can be generally obtained. Aside from the fact that diminished renal function enjoins caution, the nephritis itself would not seem to contraindicate the use of sulfanilamide, but it would seem to be the part of wisdom to be very hesitant regarding the use of the other members of this series whose tendency to cause renal damage through settling out of the acetylated product is well known.

Goldring (1941) undoubtedly expressed the consensus when he said that one should wait four to six months before removing suspected foci of infection even if they are obviously purulent; early removal invites recurrence of the nephritis.

THERAPY OF CHRONIC NEPHRITIS (AND NEPHROSIS)

Edema

High Protein Diet.—The chief surviving hypotheses in explanation of albuminuria are the two which follow. First, that functional or actual retrogressive changes in the glomerular capillaries permit the passage of albumin through this filter which normally holds it back; many observers have embraced this viewpoint. Second, that there occurs a general metabolic disturbance of such nature that there is a shift in the plasma proteins toward the coarser globulin fraction, albuminuria then resulting when the kidneys excrete this foreign "denatured" protein in a quite physiologic way and without any increase in their permeability; there is much disagreement regarding this conception at present. Fortunately, in practical therapeutics it does not really matter which of the "explanations" is the correct one, for the albumin is there in the urine regardless of how it arrived, and the patient is likewise often edematous. This association of albuminuria with edema is rather well understood nowadays: when the total protein of the plasma falls as a result of albuminuria, the ratio of albumin to globulin in the blood is reversed, the proportion of globulin to albumin becoming greater; however, the large globulin molecule exerting a lower osmotic pressure than did the smaller albumin molecule which it replaces, the total osmotic pressure within the vessels is lessened, and fluids pass out into, and remain in, the tissue spaces. This comprises the rationale of the high protein diets of today. The actual computation of diets (food value tables in Diabetes) can be based usually on the needs of a normal healthy individual of the patient's age, height and weight, though in frequent instances it may be necessary for a

TABLE 23.—HIGH-PROTEIN, LOW-SODIUM, HIGH-POTASSIUM DIET WITH ACID ASH FOR USE IN EDEMA (After BARKER)

Ingredients

Fruits:
3 servings daily, fresh or stewed, but should include either prunes, plums, cranberries or currants once daily.

Vegetables:
2 large servings daily, especially beets, carrots, Brussels sprouts, yellow corn, kohlrabi, lettuce, mushrooms, peas, spinach, kidney beans, parsnips.

Meat:
2 servings daily.

Eggs:
2.

Milk:
1 glass.

Cream:
½ glass.

Butter:
Salt-free, 6 squares.

Cereal:
Oatmeal or wheatena; farina, puffed wheat or rice occasionally.

Bread:
Graham bread, 3 large slices or 6 small slices daily.

Rice, macaroni or spaghetti:
1 serving daily.

Potato:
1 serving.

Jelly, preserves or honey:
2 level tablespoonfuls.

Sugar:
Ad libitum—at least 1 tablespoonful.

Sample Menus

1	2	3
Breakfast	*Breakfast*	*Breakfast*
Stewed currants	Plums	Stewed prunes
Oatmeal	Wheatena	Farina
Two poached eggs	Scrambled eggs	Soft cooked eggs
Graham toast	Graham toast	Graham toast
Sweet butter	Sweet butter	Sweet butter
Honey	Jelly	Honey
Cream	Cream	Cream
Sugar	Sugar	Sugar
Dinner	*Dinner*	*Dinner*
Roast beef	Broiled steak	Broiled lamb chop
Mashed potatoes	Buttered macaroni	Buttered spaghetti
Buttered beets	Stewed tomatoes	Buttered spinach
Sliced peaches	Banana salad	Grapefruit cup
Graham bread	Graham bread	Graham bread
Sweet butter	Sweet butter	Sweet butter
½ glass milk	½ glass milk	½ glass milk
Supper	*Supper*	*Supper*
Broiled chicken	Broiled liver or sweetbreads	Broiled whitefish
Buttered rice	Baked potato	Mashed potatoes
Jelly	Celery salad	Buttered Brussels sprouts
Lettuce salad	Cherries	Pineapple and nut salad
Orange cup	Graham bread	Graham bread
Graham bread	Butter	Sweet butter
Sweet butter	Jelly	Jelly
½ glass milk	½ glass milk	½ glass milk

Notes

All foods are to be prepared without salt and no salt is to be served with meals. Potassium chloride (from 2 to 5 Gm. in shaker) may be given as salt substitute. Spices—cinnamon, sage, paprika, pepper, cloves, nutmeg, allspice—may be used. Small servings of citrus fruits may be added after fluid volume is established. Additional vitamin D to be supplied in the form of viosterol.

Coffee or tea, 1 cup daily.

This diet is designed for the treatment of convalescent and ambulatory patients. Very ill patients are to be given the same foods but in smaller amounts.

time to exceed the normal daily amounts of protein per kilogram body weight. However, the optimal amount for adults seems to be between 70 and 100 Gm., for above this loss of appetite usually occurs; in children the rate of 3.2 Gm. per kilogram (2.2 pounds) of body weight seems optimal, which is also just about the amount required for proper nutrition and growth. The sample menus offered in Table 23 contain usually adequate amounts of protein; as there indicated, it should be preferably given in the form of foods with high biological value, such as meat (there are no differences between red and white meat), milk, cheese, fish, and eggs. As protein is deposited in the tissues it may increase the edema for a while until the slowly rising serum proteins (a process which may require several months) draw it out again and diuresis begins. There is no contraindication to the usual allowances of carbohydrates and fats. In many instances it is probably advisable to add supplementary vitamins. Bruger *et al.* (1939) found that alcohol in moderate amounts rarely augments proteinuria and sometimes induces moderate diuresis even in the presence of considerable impairment of renal function; in spite of these observations, however, I imagine most men will continue to feel justified in greatly restricting the use of alcohol in their patients.

Water, Salt, Acid and Base Allowances.—As above stated, edema results from the loss of proteins from the blood in a patient with albuminuria, but this is not the sole explanation for the water imbalance since it has been amply demonstrated that in renal edema a part of the water-logging is due to a retention of chlorides. Whether this retention is due to inability of the damaged kidneys to excrete these salts, or whether they are not excreted simply because they are held by the extrarenal tissues, is still a moot point. At any rate, sodium chloride when administered is retained and edema increases if the nephritic state is at all severe or advanced. An absolutely salt-free diet is certainly not advisable for the following reasons: (*a*) such a diet is woefully unpalatable and causes nausea and vomiting, headache and legache, and a host of other symptoms; (*b*) moderate reduction is easier and in the end more effective because it can be continued for a long period; and (*c*) the substitution of other chlorides is practicable to a limited extent.

The average daily salt ration in America is about 10 Gm., water intake probably 2000 cc. The salt can be considerably reduced without difficulty since most of it derives from its addition to foods during preparation, most raw foods being salt-poor. The principal exceptions that are likely to be included in the average dietary are milk, butter, cheese, preserved meats, fish and breads. Simpson wrote "In a normal diet of an average person which includes these latter articles the salt intake, exclusive of salt as a condiment, will not exceed 3 Gm. daily. The unpalatability of a salt-poor diet can be overcome, partly, by using such highly flavored substances as pepper, mustard, vinegar, lemon juice, spices, garlic, onion, etc. The rather commonly held opinion that such condiments and foods are harmful to kidney structure is not supported by experimental work." Briefly, allowing any foods desired but forbidding the use of salt either in kitchen or dining-room, means permitting 3 Gm., or perhaps slightly less, daily; this may be raised by actual additions of salt, lowered by omitting milk, salted butter or any other of the worst offending articles.

Since it is the sodium and not the chlorine retention which is of importance in edema, the practice has arisen in recent years of substituting other chlorides for sodium chloride: ammonium chloride in amounts of 5 to 15 Gm. daily,

potassium chloride, 5 to 10 Gm. daily, calcium chloride, 10 to 20 Gm. daily, or even 100 to 200 cc. daily of N/10 hydrochloric acid. Potassium chloride has had the greatest vogue but many individuals object to its metallic taste; Barker and Robinson (1938) used 2 to 6 Gm. daily of ammonium sulfate with good effect. Using a diet with a high acid ash, which is easily accomplished when high protein feeding is being employed, is also of diuretic value.

Ample experience has now shown that water restriction is not necessary for even large volumes of water given without salt are excreted without difficulty; it is the restriction of sodium salts, particularly sodium chloride, which is important, since retained sodium means retained water. Alkaline waters, such as some of the bottled waters from well-known spas, should not be allowed for their sodium content will provoke water retention.

The accompanying table (Table 23) shows the type of dietary regimen which Barker and his associates at Northwestern University use in complying with all the requirements discussed above. Briefly, the patient is given a liberal diet which is adequate in every respect except that small supplementary vitamin additions (vitamin D, in particular, is deficient) had best be made now and then. The total amounts of specific minerals agree closely with Sherman's average of 150 American dietaries except in the inverted ratio of potassium to sodium. The diet is properly high in protein and has an acid ash. No sodium chloride is used in either kitchen or dining room, but the patient is given 5 Gm., occasionally more, of potassium chloride crystals in a salt shaker each morning; with this he salts his food and at the end of the day places the remainder in water and drinks it. In the main no ill effects have followed in patients who have been upon this regimen for several years; one of Barker's patients with pronounced nephrosis required 10 Gm. potassium chloride daily to remain edema-free. Winkler *et al.* (1941) considered it unlikely that the potassium ion can cause poisoning when given by mouth under the conditions here obtaining, since they felt that even the most severely damaged nephritic kidney continues to excrete potassium. However, Keith *et al.* (1943) felt that potassium salts should not be used in patients with nephritic edema and a concentration of urea in the blood of more than 100 mg. per 100 cc., for in some of these patients there may be a lessened tolerance for potassium and even an increased value for potassium in the serum. The matter it would therefore seem remains controversial. This treatment does not alter the acid base balance.

Diuretics.—The diuretic drugs are thoroughly discussed in Congestive Heart Failure; the ones most often used in nephritic edema are potassium nitrate and a mercurial. One often hears the statement that the mercurials are contraindicated if there is renal pathology, but many leading clinicians feel that they may be used with impunity if good care is taken. Goldring (1941) said that at Bellevue Hospital they give 1 cc. of mercupurin intravenously, and if there is no diuretic effect after twenty-four to thirty-six hours another 2 cc.; if there is then no effect no further attempt is made to use the drug. However, Tyson (1941), describing two sudden and very serious (one fatal) reactions of an apparent anaphylactic nature in her own experience and mentioning three other such instances in the literature, felt that the mercurial agents are contraindicated in nephrosis. Barker *et al.* (1942), and Wexler and Ellis (1944), each reported a single fatality following the use of a mercurial diuretic in nephritis, so the score begins to pile up; however, before forming judgment it is suggested that the reader turn to

the section on the Diuretics in Congestive Heart Failure where the matter of these reactions is discussed fully.

Acacia.—In 1933, Hartmann *et al.* introduced the method of injecting acacia solution intravenously to raise the colloidal osmotic pressure of the blood sufficiently to prevent escape of fluid into the tissues. Further observation has shown, however, that this pressure usually fails to be increased, probably because the volume of circulating blood increases and the serum constituents are diluted. But nevertheless diuresis is often induced by acacia injection and therefore a new explanation will have to be found since mere increase in the volume of circulating blood will not in itself result in diuresis; there is some animal experimentation which indicates that perhaps acacia directly promotes the excretion of chlorides. Acacia lost most of its early friends very quickly because of the severe, though admittedly rare, reactions which sometimes accompanied its use, and the evidence that it is deposited, possibly harmfully, in the bone marrow, spleen, liver, lymph nodes, lungs, kidneys and edema fluid. But the agent is still very favorably reported upon by Goudsmit and Binger (1940), Lehnhoff and Binger (1942–1943), and Smalley and Binger (1944), of the Mayo Clinic, who use it very frequently in combination with a high protein diet and diuretic salts in their treatment of the nephrotic state of chronic glomerulonephritis. *Method.*—The use of potassium nitrate is begun two or three days before acacia is given and then the latter is injected slowly (forty-five to seventy-five minutes) intravenously in an average dose of 500 cc. of a 6 per cent solution in 0.06 per cent sodium chloride solution. Injections are given every day or on alternate days for at least three or four times. *Results.*—Of 40 consecutive patients in one of the reports, 36 were relieved of their edema, losing weight (edema fluid) at the rate of 1 to 3 pounds daily. Three patients who at one time responded well were not satisfactorily controlled during a relapse, though one of these responded rather promptly on a subsequent readmission. *Reactions.*—In approximately 10 per cent of the cases an urticarial reaction occurred and was controlled by epinephrine injection. Occasionally a patient complained of dyspnea or pain in the left side of the thorax during or shortly after an injection; injection was stopped and codeine given. Sometimes, too, fever occurred as after a blood transfusion. These workers recognized no contraindication to the continuance of acacia treatments except the very rare occurrence of a severe allergic reaction. They have not seen the blood pressure remain at a higher level than that which existed before the injection nor have they seen renal damage result from the use of acacia; in fact, they mentioned instances of a lowering of the blood pressure and improvement in renal function. It was their opinion that the solution can also be used without fear in patients who have severe hepatic cirrhosis.

Transfusion.—Whole blood transfusion is frequently resorted to when the edema is great enough to cause dyspnea. Diuresis and a considerable diminution of distress are often obtained, effects which may persist several days.

Serum, Plasma, Albumin and Amino Acids.—The administration of plasma has not usually induced diuresis. Aldrich and Boyle (1940) reported somewhat favorable results with lyophiled serum, but I have not seen confirmation of their findings. The injection of specially concentrated serum albumin did not induce a persistent elevation of the circulating serum albumin in Luetscher's (1944) experience; Thorn (1943) also experimented with this preparation but it was not easy to determine from his paper just what results

he obtained. Amino acids have been injected parenterally by Farr *et al.* (1940), Altshuler *et al.* (1942) and a few others, but the studies are still entirely in the experimental stage.

Thyroid Substance.—Low basal metabolic rates have been recorded a number of times in nephritis, but a reclassification of the disease which would ascribe fundamental significance to these observations is probably not warranted upon the basis of any evidence yet accumulated. In his exhaustive review, Leiter (1931) expressed doubt that the incidence of such rates is any greater than might be expected to occur secondary to undernutrition, therapeutic diets, inactivity and possibly other factors not directly related to the intimate nature of the malady.

In nephrotic cases a number of observers—Campanacci, Eppinger, Epstein, Liu, Molnar and others—have reported the favorable production of diuresis by the employment of enormous doses of thyroid substance. The results are by no means always obtained, but the fact seems to be established that individuals exhibiting the low basal metabolic phase of the malady can sometimes tolerate astonishing amounts of this ordinarily very toxic agent. Epstein gave as much as 4 Gm. (60 grains) of desiccated thyroid daily. One patient received 1.5 Gm. (22 grains) daily for five months, followed by a total of 137 mg. of thyroxin in eleven weeks, with no striking effect on the basal rate and no symptoms of toxicity. Platt failed to demonstrate thyroxin in the urine of one of the nephrotic patients while being dosed in the above extravagant manner. Leiter believes that this is not true hypothyroidism in spite of the rate, that a tolerance above normal may be found in other edematous states, and that the matters of absorption, destruction, and excretion need to be studied in view of the differences between this sort of reduced metabolism and that encountered in true myxedema. Both Mitchell *et al.* (1938) and Farr (1938) failed to find metabolic rates above normal in nephrotic children. Lueth (1941) used thyroid substance almost routinely in ½ grain (0.03 Gm.) doses three or four times daily but did not see beneficial results; Page (1940) found the drug useful only when combined with anterior pituitary extract.

Cathartics.—Some physicians favor the daily use of a saline cathartic, but the practice certainly makes it impossible to maintain any exact knowledge of the patient's ability to eliminate through the kidneys. Proprietary saline mixtures should not be used unless it is positively known that they contain no other salts than the nonabsorbable ones desired to produce the cathartic effect. The following salines are effective.

Magnesium sulfate (Epsom salt): ½ to 1 ounce (16–32 Gm.). It is worthy of note that Hirschfelder and Haury (1934) described a clinical syndrome of high plasma magnesium accompanied by somnolence and coma, which may be induced by the oral administration of Epsom salt in patients with renal insufficiency.

Magnesium citrate: principally used as the solution of magnesium citrate, an effervescing preparation in 12-ounce bottles; dose, 1 bottle or less. Milk of magnesia can be converted in part into magnesium citrate by the addition of a fruit acid, such as lemon or orange juice.

Sodium sulfate (Glauber's salt): dose, ½ ounce (16 Gm.).

Potassium and sodium tartrate (Rochelle salt): dose, 2½ drachms (10 Gm.).

Sodium phosphate: dose, 1 drachm (4 Gm.); there is also a pleasing effervescent preparation with a dose of 2½ drachms (10 Gm.).

Compound effervescing powder (Seidlitz powder): dose, the contents of one blue paper (sodium bicarbonate and Rochelle salt) and of one white paper (tartaric acid), dissolved separately in water, and then mixed.

Compound jalap powder (1 part jalap, 2 parts potassium bitartrate, flavored with ginger): 10 to 60 grains (0.6–4 Gm.) daily, stirred into ½ cup of warm water.

Mechanical Measures.—Extensive hydrothorax or abdominal ascites, if causing respiratory embarrassment, is usually relieved by paracentesis. Bland and White (1930) read a paper on the use of the Southey tubes, which provoked considerable discussion and revealed that the profession at that time at least still had considerable faith in the efficacy of mechanical drainage of fluid from the edematous legs following the opening of the skin. Several years later, Leach (1936) described an improved type of Southey tube. Goldring (1941) has expressed the belief, which is probably shared by most members of the profession, that the danger of infection with the Southey tubes is too great to warrant their employment in most instances, though I think the fact should not be overlooked that in selected cases, as suggested by Beck (1939), the judicious use of sulfonamides might considerably lessen this risk. Acupuncture (six or more punctures in either extremity with an 18 gauge needle) and the making of long deep incisions, are the older methods and have their very great efficacy marred considerably by the many obvious disadvantages associated with causing the person and bed of the patient to be soaked in fluid; for the patient able to sit up with the feet in a small tub they are excellent.

Pemberton stated his belief a number of years ago that the value of gentle massage in promoting redistribution of fluid is too much overlooked in this country. More recently Page (1940) expressed the same opinion and stated his feeling that bed rest and no exercise are inadvisable for the edematous patient unless there are absolute indications for such immobility; the latter feeling is widely shared by clinicians.

Anemia

The anemia of chronic nephritis is well known, much studied and still not understood. The latest reported investigation I have seen, that of Nordenson (1938), in Sweden, indicated that there is a depression of erythropoiesis, but a clear explanation of the cause of this depression is not revealed in the work; Townsend *et al.* (1937) considered lowered gastric acidity a contributing factor. This anemia responds very poorly to iron salts, liver and stomach preparations. Transfusions are of course frequently given but their effect is only temporary.

Hypertension

The hypertension of arteriolosclerotic nephritis is a part of the cardiovascular renal syndrome and from the therapeutic standpoint it is idle to attempt a separate consideration (see Essential Hypertension).

THERAPY OF TERMINAL NEPHRITIS

The beginning of the end is recognizable by appearance or intensification of the eyeground changes, intensification or perhaps initial appearance of hypertension, and laboratory evidences of reduction in renal function. With the approach of uremia, edema may disappear because of the destruction of so many glomeruli that a high rate of protein loss cannot be maintained;

often, however, it is replaced by the edema of congestive heart failure. In a very interesting report, Gouley (1940) described a peculiar type of myocardial degeneration which he considered characteristic of a failing heart in uremia; the pathogenesis of uremic heart failure has not been satisfactorily explained.

The chief aim of treatment at this time is to make it possible for the patient to enjoy life as much as he can until the end. Restrictions should be relaxed and the relatives told of the state of affairs so that they can help as much as possible. Page (1940) well said: "It is, I think, a therapeutic achievement when the patient walks into the hospital and dies a few days or weeks after admission."

Diet.—Nothing is to be gained by any special dietary restrictions at this stage so it is well to allow the patient to choose just about what he likes. Theoretically a moderately low protein intake would be desirable in order to keep down nitrogen retention, but as a matter of fact if insufficient protein is supplied for satisfactory tissue nutrition the balance is obtained from endogenous sources and the end result is the same as regards nitrogenous products to be eliminated. The chief problem usually is to get the patient to eat enough of anything for the appetite has usually much decreased at this stage; sometimes even the use of a small amount of wine or a cordial is justified in the attempt to promote the taking of food.

Sodium Chloride.—Often toward the end the kidneys have lost the ability to concentrate urine so markedly that large amounts of chlorides may be washed out. It is therefore well to study the plasma chlorides if possible and to administer sodium chloride (the reverse of what had been done up to this time) in an amount of 3 or 4 Gm. daily together with sufficient water so that they will be washed out and not retained to induce edema afresh. The way has to be felt carefully in each case and if there is a complicating heart failure the administration of chlorides will simply have to be abandoned.

Hypertension.—There is nothing one can do about this after it has become permanent.

Pallor.—Patients are often distressed by their ghostly appearance. Page (1940) counseled sunlight or plenteous use of the ultraviolet lamp to bolster morale.

Heart Failure.—Digitalis and fluid and salt restriction are indicated as in any other failure (see Congestive Heart Failure). The uremic patient usually tolerates digitalis or ouabain very well. It is usually considered to be undesirable under the circumstances to employ diuretic drugs.

Acidosis.—In the terminal stages of nephritis, acidosis is usually present to a marked degree. Indeed, I am sure that many observers will agree with Marzullo's (1940) statement that the severity of the symptoms of advanced nephritis and uremia is directly proportional to the degree of acidosis and not always or exactly to the extent of nitrogen retention. Phosphates and sulfates are retained in the blood, there is decreased formation of ammonia by the kidneys, and as a result direct depletion of the alkali reserve takes place. This depletion is sometimes even augmented by an increased excretion of alkali by the kidneys and the loss of additional base through vomiting, for in advanced nephritis the free hydrochloric acid in the stomach is often very small in amount.

Undernutrition is also well known to promote acidosis. Mitchell and Guest remind us of the faulty synthesis of glycogen in acidotic states as an important factor in the poor development and growth of young nephritics. Even in the

severe acidosis of advanced cases, the necessity for a too great reduction of protein will not arise if we heed the report of Lyon *et al.* (1931), whose careful work showed that the readjustment of the diet to give an alkaline ash will often result in a decrease in the acidity and considerable amelioration in symptoms; measures by which this may be accomplished are: reduction in meat, rice, macaroni, bread, cereals; increase in fruit and vegetables; addition to the diet of figs, molasses and raisins. If the patient remained on an acid diet, Lyon was able to overcome its acidifying effect, while retaining all the advantages of feeding meat, etc., by supplementing it with sufficient alkali by mouth to keep the urine alkaline; in some instances he had to do this even though a basic diet was being employed. In the presence of coma, Plotz *et al.* (1937) have given 150 to 200 cc. of 4 per cent sodium bicarbonate solution intravenously at six- to twelve-hour intervals for three or four doses.

Itching.—This is often a most distressing symptom and one difficult to relieve. Sponging, not rubbing, with a hot solution of sodium bicarbonate followed by dusting with talcum powder, or the application of 1 per cent menthol in alcohol, or an ointment of 1 per cent phenol, may be tried. Other measures are discussed under Portal Cirrhosis.

Nausea and Vomiting.—I have never seen or heard of measures really effective in checking this vomiting, though of course the whole gamut of usual procedures is run: ice-sucking, sedatives, fresh air, etc. Correction of acidosis is the best preventive.

Convulsions.—In accordance with the belief (which is probably wrong) that it is the high nonprotein nitrogen content of the blood *per se* which induces the fatal termination in uremia, sweating would be theoretically indicated because the perspiration contains 30 per cent more of these retention products than does the blood. However, even though induced only by the use of hot-water bags and plenty of blankets, sweating is a very debilitating activity. A hypodermic of $\frac{1}{12}$ grain (0.005 Gm.) of pilocarpine nitrate is very effective in bringing out the perspiration, but it also not infrequently causes vomiting and hiccup, and may bring about collapse with a very slow pulse. If there are pulmonary complications the danger of precipitating pulmonary edema with this drug is very great. If there are twitchings and tetanoid convulsive movements the possibility of hypocalcemia should be borne in mind. Calcium may be employed as in tetany, but not parathyroid extract unless the necessity seems very urgent, for there is some evidence (Highman and Hamilton, 1937) that the activity of the parathyroid glands is increased in chronic nephritis. Shelling and Hopper (1936) also advise against the use of viosterol and cod liver oil; they may raise the phosphate as well as the calcium level of the blood. Ordinary restlessness and even delirium may be combated with the sedatives and hypnotics (discussed under Insomnia), but morphine or dilaudid may have to be resorted to. Winkler *et al.* (1942) found the slow intravenous injection of 500 cc. of 2 per cent magnesium sulfate a safe procedure of some value in preventing and controlling these convulsive seizures, though they said the effects were neither certain nor dramatic following a single injection; a second injection always checked the convulsion, but after two such injections the magnesium concentration in serum sometimes became so high that its depressant effects on the nervous system were manifest. The correction of acidosis is a powerful weapon against recurrence of the convulsions. When true uremic coma supervenes there seems to be nothing to do that is worth the doing.

DISTURBANCES CAUSED BY EXCESSIVE HEAT

HEAT EXHAUSTION

This, the most common form of disturbance caused by an excessively warm environment, is known in the South as "a touch of the sun" or "overcome by the heat." There may be prodromal symptoms of weakness, headache and constipation for a few days, but usually the individual suddenly becomes acutely sensitive to the oppressive atmospheric conditions, grows pale, with a clammy skin, has disturbances of vision, feels very weak and perhaps nauseated, and either crumples down in the sun or manages to drag himself into the shade before collapsing; the pulse is fast and weak, the respirations rapid and shallow, the pupils dilated, temperature normal or subnormal, urine scant. Sometimes there are associated heat cramps (see below). Mortality from this type of heat stroke is very low, but the patient often recovers very slowly and is thereafter likely to be unusually sensitive to high temperatures. Morton's (1944) experience over a period of years in Iraq left him with the impression that the type of individual particularly prone to develop heat exhaustion is the lean, anxious, spare person with a low systolic blood pressure.

THERAPY

The patient must be taken to the coolest place available and much of his clothing should be removed. Attempt should be made to get him to drink copiously of sweetened fluids with sodium chloride added. In instances in which there has been excessive vomiting, Morton (1944) enjoined the intravenous administration of physiologic saline solution with dextrose. If the pulse remains rapid and weak for long, one of the stimulants (see Index) may be advantageously used. Occasionally in these cases the temperature falls quite far below normal and it becomes necessary to apply external heat and administer hot drinks; one should be careful here as a sudden high rise of temperature may be induced.

HEAT STROKE

(*Heat Retention*)

The severe and frequently fatal form of disturbance caused by excessive heat is characterized by a brief prodromal period not easily distinguishable from that occurring in ordinary heat exhaustion (see above), but consciousness is early lost and it is noticed that the skin, instead of being clammy, is dry and hot and that the temperature is very high. The pupils are usually dilated in the beginning, but the pulse is rapid and full and the breathing deep. It is only later that the pulse becomes irregular and feeble and the respirations become shallow and finally of the Cheyne-Stokes type; at this stage the pupils

are found to be contracted and the conjunctivae injected. In many cases involuntary passage of characteristically foul feces takes place and the patient's body odor also becomes offensive. Muscular twitchings and rolling of the head are common; sometimes epileptiform convulsions take place. As death approaches evidences of pulmonary edema are sometimes to be found. All observers have noted that individuals in poor general condition are extremely prone to this type of heat stroke; Bulmer (1943) reported that in Libya all the patients sent to his hospital with this diagnosis were found to be suffering from malaria, pappataci fever, or sepsis. Old age and acute alcoholism seem also to predispose very markedly to heat stroke; Morton (1944) gained the impression from his experience in Iraq that the obese, thick-necked individual with a high systolic blood pressure is the type most likely to develop heat stroke.

Tenner (1942), and Buss (1943), each described single cases in German soldiers, and Freeman and Dumoff (1944) two cases in American civilians, in which permanent central nervous system residuals followed recovery from severe heat stroke.

THERAPY

It is imperatively necessary to reduce the temperature of this patient as rapidly as possible; Morton (1944) said that although short periods of temperatures as high as 112° F. (44.4° C.) or more have been followed by recovery, he was doubtful that if the temperature had remained at 108° F. (42.2° C.) or over for more than two hours survival could take place. The patient should be encouraged to drink large quantities of fluids containing glucose and sodium chloride, but Morton felt that since these patients are not usually dehydrated and are often suffering from a failing circulation the decision to use intravenous saline should be very carefully weighed. Oftentimes the use of cardiac and respiratory stimulants is required, and it is sometimes necessary to administer chloral and bromide by rectum to control the convulsions. Both Corr (1942) and Morton (1944) recorded single cases in which the withdrawal of spinal fluid controlled the convulsions. The principal methods of effecting a quick lowering of the body temperature are the following:

(*a*) Water is sprayed onto the body from a fine nozzle preferably, or it may be frequently sponged over the body, meanwhile maintaining a constant current of air either by means of hand or electric fans. There is no great advantage in using ice water as tepid water will remove nearly as much heat. This method has replaced all others in most hospitals and has the great advantage that it can be utilized anywhere since it does not depend upon the use of ice. When the rectal temperature reaches 102° F. (38.8° C.) evaporation may be stopped during a period of observation. The experience of Hearne with the British troops in Mesopotamia in War I has been amply confirmed in War II, namely, that the cessation of sweating once it has been established is a valuable sign of impending recurrence, and that if these patients are covered with a moist sheet and the fanning resumed, artificial perspiration will be established and recurrence sometimes averted.

(*b*) In this method the patient is placed in water cooled to 50° F. (10° C.) by floating a cake of ice in it, and he is kept there until the rectal temperature falls to 102° F. (38.8° C.). After this temperature is reached the body will continue to lose heat in favorable cases even after removal from the water; sometimes the fall will go below the normal line. It is imperative that

vigorous manual friction of the skin be made continuously while the patient is in the tub, for unless hyperemia takes place the overheated blood will only be driven in instead of being cooled at the surface. In a study of 44 cases of severe heat stroke during a short severe heat wave in Cincinnati in 1938, Ferris *et al.* found ice water tubbing with massage the most satisfactory first method of approach.

(*c*) Injection of 1000 cc. or more of ice water into the rectum. This method is very little employed in the large clinics where many of these cases are seen each summer in civilian life; Morton's objection to the ice enema is that it deprives one of the use of the rectal thermometer and is also theoretically liable to increase shock.

(*d*) Rubbing the body with ice, or placing the patient in sheets wrung out of ice water. These methods are considered much less satisfactory than any of the above; indeed, Elkins, reviewing the subject in 1938, went so far as to say that ice water baths, ice water enemas and packs should never be used.

Recurrence of heat stroke is by no means uncommon. Morton found the use of magnesium sulfate enemas to relieve headache in convalescence of considerable benefit, particularly in those patients whose cerebration was slowed and in whom there was no evidence of dehydration. He warned that if the patient has been treated in an air-conditioned ward transition from it to an ordinary ward should be a very gradual one. It is the consensus that at least three weeks should elapse before a patient is allowed to travel or to resume activity, and in many instances in military practice it has been found necessary to transfer the soldier to a cooler climate in order to effect recovery.

THERMOGENIC ANHIDROSIS

Wolkin *et al.* (1944) described an interesting syndrome differing from heat stroke and heat exhaustion which was seen by them in American soldiers undergoing training in the desert area. The attack typically began with a rather sudden onset of generalized weakness, subjective warmth and discomfort, dizziness, headache, and shakiness, the symptoms occurring during exposure to sunlight either with or without physical exertion. These symptoms were associated with or preceded by a cessation of sweating in each case, which in turn was often preceded by a distinct period of profuse perspiration from a few days up to several weeks duration. The loss of sweating was limited uniformly to the body region below the neck in pronounced contrast to the outpouring of sweat from the face and neck. The skin of the entire body below the neck in addition to being warm and dry had the appearance of goose flesh, though the eruption did not appear and disappear in a matter of minutes as goose flesh does; in cases of long standing there was a fine branny desquamation. The body temperature in these cases for the most part remained normal orally except when the external environmental temperature reached heights of 120° F. or over; under these conditions there were complaints of extreme feeling of heat, discomfort and irritability. Ladell *et al.* (1944), describing a series of similar cases seen in Iraq, noted in most instances the added symptom of polyuria.

THERAPY

It was found that the only successful management of these cases was to effect their immediate removal from the excessively warm region. The use of salt solution was not found to be of value. It was stressed that these individuals should avoid exposure to excessive heat until the sweat function has returned to normal; indeed, Wolkin *et al.* were inclined to oppose a return to similar climatic conditions even then.

HEAT CRAMPS

(*Stokers' Cramps*)

This is a type of heat exhaustion seen frequently in those who labor in the heat of firerooms, in deep mines, etc. Following a period of muscular twitching, the patient is seized with violent cramps principally of the abdominal groups; sometimes, however, the spasm is so general as to resemble an epileptic attack. The patient is nauseated, dizzy, stuporous, and usually pallid and perspiring; the pulse is rapid but strong and the temperature little if at all above normal. Urine is scanty and there is usually great thirst. These attacks are believed to be due to the fact that in the excessive ingestion of water and its elimination through the skin abnormal quantities of chlorides are lost, though just why this loss of chlorides should cause the cramps is not clear. Loss of vitamins in the sweat is insignificant with the possible exception of nicotinic acid (niacin).

THERAPY

The sufferer must be removed to the coolest place available and be allowed complete rest. The opiates are almost completely ineffective in lessening the cramp or pain, but rest alone suffices in most instances. Talbott (1935), reviewing the literature, his experience with Michelsen during the construction of Hoover Dam, and his own observations in the Youngstown mills, stated that the only reliable as well as rational remedy in severe cases is the intravenous administration of physiologic saline solution, 600 to 1000 cc., and repeated if the patient is much dehydrated. Thereafter 15-grain (1 Gm.) salt tablets are given by mouth every hour until fifteen have been taken; or the patient is put on an exclusive diet of milk, in large quantities, for twenty-four hours.

Prevention consists merely in the ingestion of sufficient salt, though the mistaken idea that dextrose is protective is apparently widespread. Salt may be taken in the form of a 15-grain (1 Gm.) tablet each time water is drunk. Most workmen object to swallowing the tablets, however. Talbott stated that the best way of supplying salt is to place it in the drinking water in a concentration of 0.1 per cent; he says that such a solution does not have a perceptible saline taste and allays rather than promotes the sensation of thirst. MacLean (1943), describing his experience on a British cruiser during War II, said that ten times this much salt (a teaspoonful to the pint of water) was found to make quite a palatable drink provided the water was ice cold.

All classes of individuals subject to heat cramps by the nature of their occupation themselves realize that the better their general physical condition the less likely they are to develop this syndrome.

THE ANEMIAS

So much progress has been made in hematology in recent years that the hallowed separation of all anemias into "primary" and "secondary" types has had to be superseded by more rational classifications. Undoubtedly the most useful of these for scientific purposes approaches the subject from the standpoint of the size and color of the erythrocyte as indicative of the pathogenesis of each of the maladies; but I doubt if such a classification has as yet been perfected to the point of being of greatest therapeutic service. Therefore in this chapter I am considering the several anemias according to an arrangement designed to facilitate and expedite their satisfactory treatment.

ANEMIAS PRIMARILY BENEFITED BY IRON THERAPY

Nutritional Anemia of Infants.—The normal infant, born into the world with many more erythrocytes and much more hemoglobin than is needed for extra-uterine life, rapidly and proportionately loses both (icterus neonatorum often evidencing the destruction that is going on) for about six weeks, and more slowly to about the tenth week, after which the values slowly rise again to the fifth or sixth month. This period of "physiologic" anemia usually requires no treatment, but the abnormal condition of the blood frequently seen in infants between six months and two and one-half years does call for the institution of therapy. It is a true anemia in which, though the erythrocyte count may be high, low, or normal, the cells are smaller than normal (microcytosis) and are subnormal in hemoglobin content (hypochromia), and there is a low hemoglobin content of the whole blood. Enlargement of liver, spleen and lymph nodes, and slight edema of the extremities, are sometimes seen, but the youngster usually appears to be in a good state of general nutrition; pallor is of frequent occurrence but alone does not necessarily indicate the presence of this type of anemia. Gastric acidity is sometimes decreased. The low iron content of human and cow's milk is responsible for the malady, which will appear (*a*) if the amount of iron stored in the fetal liver during intra-uterine life has not been sufficient to carry the infant until mixed-diet feeding can begin, or (*b*) if the mother has received insufficient iron in her dietary during pregnancy, or (*c*) if the infant is one of twins or is born prematurely.

Nutritional Anemia of Wartime.—In Britain, Mackay *et al.* (1942), Sinclair *et al.* (1942), and Davidson *et al.* (1943) offered some evidence of a general lowering of hemoglobin values during War II and generally attributed it to a dietary deficiency of iron. However, Findlay's (1942) findings and opinion were not entirely in accord with that of the other workers, and therefore the matter of this alleged occurrence of wartime iron deficiency is controversial. In the most recent report of Davidson *et al.* (1944) marked improvement in the situation was noted.

Chlorosis.—This disease, usually thought to have quite generally disappeared, has the following characteristics: (*a*) occurrence practically exclusively in girls of the servant class between puberty and twenty-five years of age; (*b*) anemia characterized by moderate or perhaps no reduction in the number of erythrocytes but with a variable reduction in their size and a hemoglobin content so low that in a stained preparation the cells appear definitely achromic, often being mere rings; there is frequently a striking thrombocytosis (*c*) greenish pallor, most marked about the eyes and chin; (*d*) the usual signs of severe anemia, such as breathlessness, irritability, and edema of the extremities, and often, in these cases, puffiness of the face; (*e*) constipation and dyspeptic disturbances, perverted appetite, low-grade fever, and often irregular or scanty menses. Recent reviews indicate that hyperacidity was not so regularly present as had been believed. Nowadays it is recognized that a large number of these girls certainly had peptic ulcer or tuberculosis. Very interestingly, Patek and Heath (1936) stated that chlorosis has not disappeared, reporting 4 cases that had entered their clinic in the preceding two years; Olef (1937) was also able to report 3 cases recently seen. Patek and Heath defined the malady as merely the exaggeration of a normal tendency toward anemia in adolescent girls, created by the increased demand for iron made by growth and by menstrual or other blood loss, and by diet deficient in iron-containing foods; and they reminded us that Stockman very soundly pointed out these things as long ago as 1895.

Idiopathic Hypochromic Anemia.—This entity has been recently described under a variety of names: achylic chloranemia, simple achlorhydric anemia, idiopathic hypochromemia, hypochromic anemia with achlorhydria, primary hypochromic anemia, chronic chlorosis. Most of the patients are women between the ages of thirty and fifty years, though the disease is not unknown in men; Thomson (1943) reported 9 cases of what seemed to be idiopathic hypochromic anemia in adolescent male recruits in England. There is a host of symptoms, which probably prevented the earlier recognition of the syndrome as a unit; however, the principal ones are partial or complete achlorhydria and achylia, anorexia, tongue appearance like that in pernicious anemia, paresthesias and other nervous changes (if there is difficulty in swallowing—probably due to esophageal spasm—one speaks of the Plummer-Vinson syndrome), fingernails and toenails with spoonlike depressions, enlargement of the spleen in one third to one half of the cases, discomfort and flatulence following meat so that carbohydrates are mostly eaten, possibly diarrhea, menstrual disturbances, systolic murmurs over the whole precordium and perhaps some degree of cardiac dilatation, pallor, chronic fatigue, a blood picture practically indistinguishable from that of chlorosis, and a history which reveals the symptoms to be of long standing.

Fowler and Barer (1937) concluded that this is usually a chronic hemorrhagic anemia due to menstrual blood loss and an improper absorption of iron due to deficient gastric secretion. Meyers *et al.* (1938) found one or other of the following factors in the probable etiologic role in many of their cases: deficient meat and iron intake, deficient gastric acidity and other digestive disturbances, hypothyroidism, multiple pregnancy, menorrhagia and other forms of bleeding; they classified 24 per cent of their patients as constitutional psychopathic inferiors. Lundholm (1939), in an extensive study of the subject in Sweden, recognized hemorrhage as important in the development of this anemia but was unable to correlate the amount of blood lost at menstruation

with the degree of anemia; very interestingly, however, he felt that there is an hereditary factor concerned in the etiology.

Anemia of Gastro-intestinal Surgery.—The majority of the cases of anemia following gastrectomy and gastro-enterostomy are of the simple hypochromic type just described above.

Anemia of Chronic Blood Loss.—The rate at which the erythrocyte and hemoglobin content returns to normal in a healthy person after a single severe hemorrhage varies widely with individuals, but in perhaps most instances cell return is completed in four to six weeks with pigment return in six to eight weeks. Neither iron nor liver administration is indicated in these cases ordinarily; the presence of chronic infection will considerably retard recovery. Patients chronically bleeding oftentimes present the picture of a severe hypochromic-microcytic anemia—the type in which iron, but not liver, is strongly indicated.

Anemia of Pregnancy.—Pregnancy may of course supervene upon any of the anemic states, and in itself may be responsible for anemia following hemorrhage or incident to toxemia or sepsis; but excluding these things, there are anemias of quite other causation. One of these is seen with such regularity that it has come to be called the "physiologic anemia" of pregnancy: a steady decrease in both erythrocytes and hemoglobin to about the end of the second trimester. Increasing knowledge of blood volume changes has now shown this to be only a reflection of hydremia—dilution of the blood causes it to appear poor in cells and hemoglobin. The true (and they are often severe) anemias were shown by Strauss and Castle, in 1932, and by others since, to be almost always of the hypochromic type described above and to occur as the result of a direct dietary deficiency or a deficiency consequent upon impaired gastric secretion. Rarely, the anemia is of the macrocytic type benefited by liver therapy, which is discussed later under the Miscellaneous Macrocytic Anemias.

Hookworm Anemia.—In the anemia consequent upon ancylostoma infestation, which is really an anemia due to chronic blood loss, the erythrocytes are markedly reduced in number and in size; hemoglobin is diminished to an even greater extent proportionately. This is, then, a hypochromic-microcytic anemia such as the others already discussed, and it improves quickly and regularly on iron medication without any additional treatment and even before deworming. Heilig and Visweswar (1942) pointed out that when quick response to iron therapy is not obtained in these anemias, the other infectious diseases which patients in regions of heavy hookworm infestation are likely to have—malaria, and the like—should be treated simultaneously with the administration of the iron.

THE ADMINISTRATION OF IRON

It seems that the upper part of the small intestine is the chief site of iron absorption and that the soluble ferrous salts are the most easily absorbed and assimilated; indeed it is probable that all other forms of iron must be reduced to the ferrous state before their utilization becomes possible. The nuclei of erythroblasts in the bone marrow take up the iron conveyed thither in the blood plasma; when hemoglobin has been formed from it the nuclei are extruded and the "mature," non-nucleated, hemoglobin-bearing erythrocytes pass into the circulation. Under the influence of iron there is an increased rate of delivery of erythrocytes from the marrow for a time, and

even reticulocytes—the last stage before full maturity—enter the blood stream; in the early stages of iron therapy the reticulocyte count affords an index of the patient's response to treatment. It is usually felt that average hemoglobin regeneration occurs at the rate of 1 to 2 per cent per day, the height of the effect being reached between the twenty-fifth and fortieth days. But dosage must be correct, for there is a definite "threshold" which must be passed before response is obtained. All the signs and symptoms of anemia may be caused to disappear, but the ability to secrete hydrochloric acid will rarely be restored if it has been completely absent. When iron is subsequently omitted the patient is extremely likely to relapse no matter how large an amount of the metal has been stored. It would seem that this sequestered iron constitutes, in the words of Witts (1936), "a frozen credit which they cannot liquefy."

Choice of Preparation.—General intoxication from the administration of iron by mouth practically does not occur (only 1 case has been recorded: Hurst, 1931); the drug may be given by mouth even to patients with a

TABLE 24.—IRON SALTS FOR ADMINISTRATION BY MOUTH

Salt.	Daily dosage.		
	Adult.	Children.	Infants to 4 yrs.
Ferrous sulfate	12 grains (0.8 Gm.) or more	10–12 grains (0.6–0.8 Gm.)	6–8 grains (0.4–0.5 Gm.)
Reduced iron	45 " (3.0 ")	.....	.....
Ferrous carbonate (Blaud's pill)	60 " (4.0 ")	.....	.....
Ferric ammonium citrate	90 " (6.0 ")	60–90 grains (4–6 Gm.)	15–45 grains (1–3 Gm.)
Ferric pyrophosphate	.....	.....	2½ grains (0.15 Gm.)

bleeding peptic ulcer or with ulcerative colitis. Effective doses cannot be given parenterally, however, without incurring the great risk of a severe reaction (too little work has as yet been done with the iron ascorbate of Friend [1938] to constitute a contradiction of this statement). We shall therefore consider only preparations for peroral administration, and of these only those which are most favored by leading students of anemia (Table 24). It is best in using any of them to begin with small doses and take several days to work up to full doses, thus lessening the likelihood of gastro-intestinal upset.

Ferrous Sulfate.—Since the human seems to absorb ferrous much more readily than ferric iron, this would seem to be the most desirable preparation to use; it is certainly the least likely of all the salts to cause gastro-intestinal irritation especially if given just after meals. The usual practice is to have one dose taken after each meal and one on retiring. Ferrous sulfate oxidizes to the less effective ferric compound when exposed to air, but the 3-grain (0.2 Gm.) coated commercial tablet is stable. Mackay and Jacob (1937) found that the salt keeps more than two months at room temperature if mixed in solution

with dextrose and a small amount of hypophosphorous acid; the following prescription may be written for an infant:

℞	Ferrous sulfate	ʒiss	6.0
	Dilute hypophosphorous acid (U.S.P. IX)	♏xv	1.0
	Dextrose	℥ij	60.0
	Chloroform water to make	℥viij	250.0

Dissolve the dextrose and ferrous sulfate in separate portions of chloroform water, then add the acid to the dextrose portion. Mix the two portions and make up to volume with chloroform water.

Label: 1 teaspoonful four times daily in water, milk, or fruit juice. (The teaspoonful will contain 1½ grains, 0.1 Gm.)

There is also commercially available an elixir of ferrous sulfate; Reznikoff (1944) said that the adult should be built up to a dose of three teaspoonfuls (about 12 cc.) three times daily after meals. It is best not to use iron in solution in treating adults as it may stain the teeth even though taken through a tube; however, the discoloration is superficial and may be removed by thorough "cleaning" of the teeth by a dentist.

Ferrous Gluconate.—Reznikoff (1944) said that most of the few individuals who are intolerant to ferrous sulfate can take ferrous gluconate in fairly adequate amounts. He starts with one 5-grain (0.3 Gm.) tablet after each meal and increases this gradually until the patient is receiving nine tablets a day unless gastro-intestinal symptoms occur.

Reduced Iron.—This drug is insoluble and must therefore be given in capsule form; it can be suspended, of course, but the offering of such a forbidding dose to the patient is inexcusable; of course for infants one can prescribe any of the iron salts in capsules and then empty the contents of a capsule into orange juice which is well stirred while being drunk. Any older child or adult can easily swallow a capsule containing 7½ grains (0.5 Gm.) of reduced iron. The average adult dose would require the taking of 6 such capsules during the day. Warrant for the contention that this preparation is best taken before meals would be difficult to produce, I think, for so many of these patients are achlorhydric.

Pill of Ferrous Carbonate (Blaud's Pill).—The coated pills nowadays obtainable keep well enough, but they tend to become very hard and doubtless sometimes pass through the intestinal tract undissolved; some men have them powdered by the druggist and packed into capsules (it is well to provide one capsule per pill). Ferrous carbonate does not tend greatly to disturb the gastro-intestinal tract, but the patient must take 60 pills daily in order to receive full adult dosage.

Ferric Ammonium Citrate.—This salt must be given in high dosage and gastro-intestinal irritation from it is not unusual. It is very soluble and may well be prescribed as follows for the adult who would require the average full dose:

℞	Ferric ammonium citrate (powdered)	℥ij	60.0
	Syrup of cinnamon (N.F.) to make	℥viij	250.0

Label: 2 teaspoonfuls in water, milk, or fruit juice three times daily. (The teaspoonful will contain 15 grains, 1 Gm., of the iron salt.)

This preparation is perhaps more likely to stain the teeth, even though taken through a tube, than is the solution of ferrous sulfate. Ferric ammonium citrate may also be prescribed in capsules; one of convenient size will hold 4 grains (0.25 Gm.).

Ferric Pyrophosphate.—Elvehjem (1937) used this preparation satisfactorily in infants; it seems to have the advantages of being quite soluble, practically tasteless and not astringent. A prescription employing it will be found below.

Potentiation of Iron with Copper, Acid, Liver, Vitamins and Other Substances.—Convincing evidence has not been offered that the addition of copper to iron therapy is of any value in the iron-deficiency anemias of adults; indeed Fowler and Barer (1941) seem positively to have shown that it is not. But the investigations of such workers as Elvehjem *et al.* (1935–1937), Usher *et al.* (1935), Josephs (1931), and Hutchison (1938), indicated that in some instances of nutritional anemia in infants the addition of small amounts of copper to the iron will cause the maximum regeneration of hemoglobin. Many American pediatricians hold the view expressed by Smith (1936), that although the same results may probably be accomplished by substituting another iron salt, or increasing the dose of the original preparation, the introduction of a small copper supplement should be kept in mind when simple nutritional anemia becomes refractory. Some continental and British students do not feel, however, that copper is of value under any circumstances. A few men think that copper ingestion may incline individuals toward the development of hemochromatosis, but they are probably wrong. An amount of copper sulfate which will give $\frac{1}{20}$ grain (0.003 Gm.) to the dose—3 grains (0.18 Gm.) added to any of the preceding 8-ounce (250 cc.) prescriptions—may be used, or the following prescription which I have modeled upon the solution used by Elvehjem may be written:

℞	Ferric pyrophosphate	ʒiiss	10.0
	Copper sulfate	gr. iij	0.18
	Alcohol	ʒiij	12.0
	Cinnamon water to make	℥viij	250.0
	Label: 1 teaspoonful *daily* in milk or fruit juice.		

There have been some indications that other elements, particularly manganese, germanium, cobalt and calcium, and also the substance chlorophyll, have some influence upon iron utilization, but as yet no practical applications that are convincing have been offered. The study of Patek and Minot (1934) suggested that in certain cases of iron-deficiency anemia in adults there may be also a deficiency in some useful material contained in bile pigment; but I have heard nothing further of this.

Since iron seems to be either better absorbed from an acid than from an alkaline medium, or is absorbed in a more readily available form, and since many patients with one or other type of iron-deficiency anemia are also deficient in gastric acid, the assumption is quite naturally made that hydrochloric acid should be administered as in the treatment of hypochlorhydria *per se*. The fact of the matter is, however, that no clinical study has ever convincingly shown that such therapy has value from the standpoint of increasing the effective utilization of iron; the latest study of this nature that I have seen (Pohle and Heath, 1939) indicated that neither acid nor alkaline salts in large amounts affected the utilization of iron. In some instances acid may undoubtedly help allay the dyspeptic symptoms which frequently afflict these patients; but it may also aggravate these symptoms.

Patients with the iron-deficiency anemias do not ordinarily profit by the addition to the iron regimen of the liver and stomach preparations used in pernicious anemia, or of the so-called "secondary anemia liver extract."

Castle and Minot (1936) wrote: "We have never observed a case of hypochromic anemia which would not respond to iron, but which would respond to whole liver or to some fraction of liver." They added that in rare instances iron alone will not bring the hemoglobin quite up to normal and that the addition of liver in these cases will do so, but that also the use of a proper diet will serve as well. Dameshek (1945) states unequivocally that liver has no effect whatever even of an additive type. However, it should be remarked that Hartfall's (1934) study of postgastrectomy and gastro-enterostomy anemias indicated that it may sometimes be profitable to consider these cases as partaking of the features of both hypochromic-microcytic (iron-deficiency) and hyperchromic-macrocytic (liver-stomach deficiency) anemias, and treat accordingly.

The allegation that vitamin B complex aids in iron absorption and utilization seems to have been disproven by the study of Moore *et al.* (1943). In their 32 patients with hypochromic anemia in whom nicotinic acid (niacin) deficiency, ariboflavinosis, or multiple neuritis were also present, iron therapy alone produced satisfactory reticulocyte response and rate of hemoglobin regeneration and the addition of brewer's yeast had no demonstrable effect in increasing the efficacy of iron therapy. Sinclair (1942) stated the feeling that possibly the reduced intake in vitamin C by the population might in some degree account for the alleged increase in nutritional anemias occurring in England during War II, but Yudkin (1942) pointed out that it has been shown in the British Navy that the addition of vitamin C to the diet did not produce any change in hemoglobin values; Davidson and Donaldson (1944) also found that supplementing iron therapy by the daily administration of 25 mg. of ascorbic acid did not raise the hemoglobin levels in their study of iron-deficiency anemias in school children.

Dietetics.—Nowadays, infants are got onto solid foods much more rapidly than used to be the case: cereals (pablum is said to be high in iron) at the third month; eggs, fruits, and puréed vegetables between the fifth and seventh months; meat at ten months. In addition to supplying muscle- and bone-building substances, and vitamins, such a well-rounded dietary also keeps pace with the need for iron. But as a matter of fact we do not know just which foods are the best from the latter standpoint. Of course elaborate tables of the iron content of foods are available, but studies in recent years have shown that the iron content of a food and the availability of that iron for hemoglobin production are often quite different things. It will require much laborious work still before we shall be able to say precisely that this or that article of food is to be preferred for its contribution of iron. Such dietary procedure for infants as that indicated above, and for adults insistence upon the liberal use of red meat, eggs, green vegetables and fruits, remain our best guides; but dietary measures alone are of practically no value in combating this group of anemias—the carefully studied patients of Mettier *et al.* (1933) failed to be benefited in the least by an "iron-rich" diet taken for a long time, but the bone marrow responded rapidly and excellently when large doses of iron were added. Likewise the study of Brokaw *et al.* (1942) showed that the early introduction of cereals, vegetables and eggs had no marked effect on the hemoglobin level or the red blood count of infants.

Routine Administration of Iron in Pregnancy.—A number of modern studies has been increasingly indicating the advisability of the routine employment of iron after the middle of pregnancy; that of Bethell *et al.* (1939)

is a recent example. Not all obstetricians agree on the point, however, for some, like Labate (1939), believe that since only 50 per cent of women develop anemia during pregnancy it is sounder practice to check the blood status several times during the period and give iron only when indicated. Nevertheless, the evidence of Corrigan and Strauss (1936) in favor of routine use of iron seemed rather convincing. One hundred members of a group of 200 normal pregnant women were given iron, the alternate 100 being used as controls; observations began when the women were from three to seven months pregnant, the average one hundred and sixty-two days. There were no important dietary or blood-level differences between the two groups. Determinations one week postpartum revealed that in the treated group (*a*) the hemoglobin average was 85 per cent (a gain of 12 per cent over their average in the beginning); (*b*) none of the women had a hemoglobin below 70 per cent; (*c*) the erythrocyte count had risen from 3.72 to 4.28 million per cubic millimeter. In the untreated control group: (*a*) the hemoglobin average was 75 per cent (just what it had been at the beginning); (*b*) 24 per cent had a hemoglobin below 70 per cent; (*c*) the erythrocyte count had risen from 3.88 to only 3.94 million per cubic millimeter.

Routine Administration of Iron in Infancy.—Mackay, in England, is well known as a champion of the opinion that routine iron therapy in the latter months of pregnancy is not enough, and that, at least in the inhabitants of an impoverished area, routine dosing of infants with iron is also urgently needed. Here and there voices are in agreement with her, but nothing to speak of is done in the matter, I believe.

Routine Administration of Iron to School Children.—In large-scale studies in England during War II, Davidson and Donaldson (1944) found that the hemoglobin level of school children was often below normal and that the administration of even such small amounts of iron as represented in 3 grains (0.2 Gm.) of ferrous sulfate once daily for five days a week could produce a significant rise in the hemoglobin levels. One is certainly unwarranted however in drawing a conclusion from this observation that the routine administration of iron to children in the school years is a necessary or advisable procedure.

Transfusion.—In these days of furious speed—"super" trains and airplanes, pictures from the battle fronts before the ship has gone down or before the land engagement has fairly begun, and so on—there is burgeoning a school of impatient therapists who can wait for nothing. To a man, these chaps fume for blood transfusion in the anemia of pregnancy—if the husband can afford it.

ANEMIAS PRIMARILY BENEFITED BY LIVER-STOMACH THERAPY

Pernicious Anemia.—Pernicious anemia is a chronic deficiency disease which progresses, usually with remissions, to a fatal issue unless we supply the patient adequately with a certain specific substance which his own economy has failed to produce, in which case the chief manifestations of the disease can be held in abeyance apparently for an indefinite period of time. The outstanding feature of the disease is the peculiar macrocytic-

hyperchromic anemia, accompanied by thrombocytopenia and the appearance of numerous many-lobed polymorphonuclear cells, though there is usually an absolute leukopenia and neutropenia. The number of red cells is usually below 2,000,000, counts of 500,000 or less not being unusual. Hemoglobin is somewhat reduced but not in proportion to the reduction in the number of red cells; consequently there is always a color index higher than one. In addition, there is marked anisocytosis with macrocytes predominating, marked poikilocytosis, and diffuse and punctate polychromatophilia. A variety of nucleated red cells, and occasionally mitosis, are seen. (Warning: gastro-intestinal carcinoma can give a blood picture astonishingly like this!) In the beginning of a remission there is an increased number of reticulated red cells. The findings of Dameshek and Valentine (1937), and of Stasney and Pizzolato (1942), show that the changes in the marrow are accurately portrayed by this picture of arrested maturation and malformation presented in the peripheral circulation. The van den Bergh (indirect) reaction is increased. Very interestingly, Warner and Owen (1942) found that patients in relapse frequently show considerable decrease in plasma prothrombin, this hypoprothrombinemia not responding to the administration of vitamin K but disappearing when specific liver therapy is instituted.

Symptomatically the onset is insidious, the patient usually appearing for the first examination with most of the characteristic symptoms present in some degree. There is complaint of languor, muscular weakness and shortness of breath on exertion. As a rule there is little or no weight loss in the beginning, but if the gastro-intestinal symptoms are marked the patient not infrequently becomes thin. In these days of earlier diagnosis the characteristic lemon-yellow tint to the skin is seen less often than a simple pallor. A heart murmur of the "hemic" type is almost the rule, and symptoms of angina pectoris are sometimes quite prominent. Slight puffiness of the ankles is a frequent finding; in rare cases the edema is much greater. Carter and Traut (1943) found some type of cardiovascular manifestation in 257 of their 300 cases. Fever, or the opposite, a subnormal temperature, may characterize a severe relapse. And then there are, in addition, the gastro-intestinal and central nervous system symptoms. The former may at one time or another include all the dyspepsias, with periods of diarrhea or apparent gallbladder disturbance being especially prone to occur; tongue and stomach findings are the most constant. The tongue is, off and on, sore and raw, particularly around the edges, and may at times be slightly ulcerated; it is nearly always smooth, red and glazed, and without any furring. The chief finding of moment in the stomach is a great diminution in hydrochloric acid; in fully established cases, with extremely rare exceptions, there is a constant achylia—indeed Askey (1944), after reviewing 47 reported cases of supposed pernicious anemia without achlorhydria, concluded that until precise critical tests have proved that acid secretion can persist in pernicious anemia, the presence of acid in any case must be considered as ruling out addisonian pernicious anemia. Careful examination will reveal involvement of the central nervous system in at least 80 per cent of cases. Paresthesias are most frequent, but diminution in the objective senses, such as to vibration and posture, and other evidences of posterolateral sclerosis are not unusual; indeed it is the consensus that in the absence of ergotism, syphilis, pellagra, arteriosclerosis and cachectic states (in all of which, as a matter of fact, the anatomic changes are distinctly different from those in the sclerosis of pernicious anemia), all cases of subacute

combined degeneration of the cord are in reality cases of pernicious anemia. However, Palmer and Porter (1936) reported 1 case, and Suh and Merritt (1938) 8 cases of such degeneration without the typical blood findings of pernicious anemia; Palmer and Porter's patient experienced a prolonged spontaneous remission of symptoms, and 4 of the 6 patients treated in Suh and Merritt's series responded well. Except for the changes in the cord, central nervous system involvement is rare though pernicious anemia patients are generally irritable and extremely difficult to handle; definite psychoses are occasionally encountered—Adams and Kubic (1944), analyzing the reported cases, including 2 of their own, found that patients with brain lesions have mental symptoms but that cerebral lesions are not always found in cases in which mental symptoms have been present. In some instances the occurrence of neurologic signs precedes other manifestations by a considerable period; Sanford (1935) reported 3 cases in which prompt liver therapy entirely prevented the appearance of hematologic evidences of the disease; perhaps Palmer and Porter's and Suh and Merritt's cases, mentioned above, could be simply explained on this basis. Bigg (1940) has shown that splenomegaly is rare nowadays, for in a series of 200 consecutive cases the spleen could be palpated in only 3 per cent. Marked enlargement of the liver is not frequently noted in the living patient, but at autopsy both the organs are found to be somewhat enlarged. Other constant findings at autopsy are the extension of hyperplastic red bone marrow into portions of the medullary cavity of the long bones ordinarily occupied by fat only; the "tiger lily" appearance of the heart; the presence of hemosiderin granules in a number of the organs; and, in many cases, the presence of foci of sclerosis in the cord and sometimes in the brain also. Marked atrophy of the gastric mucosa is said to be characteristic, but Jones, Benedict and Hampton (1935) were led to believe by their studies in the living—direct, gastroscopic, roentgenologic and biopsy observations—that atrophy is not an invariable accompaniment of the disease but occurs particularly during a relapse; Magnus and Ungley (1938) found lesions in all their 7 autopsied cases which they thought were to be regarded as atrophic processes and definitely not the end-result of an inflammatory gastritis—however, all of the 9 untreated patients examined gastroscopically by Schindler and Serby (1939) presented superficial gastritis, superficial plus atrophic gastritis, or patchy or diffuse atrophy.

This type of anemia occurs among rich and poor alike, among urban and rural dwellers regardless of type of occupation. Only a few cases have been reported in infancy, childhood and adolescence, and the malady is very rare between twenty and thirty, but after this latter age the incidence increases rapidly up to the age of seventy, and then again it is rare in extreme old age; in the 80 cases studied by Hardgrove *et al.* (1944) the highest incidence occurred in the seventh decade although the extremes in the series were thirty-seven and eighty-three years. There has come to be more than a suspicion of familial and hereditary tendencies. In the United States, England and France, more men are affected than women, but in Germany, Finland and Scandinavia the reverse seems to be true. Classical addisonian pernicious anemia is very rare in the tropics. Most of those who have this disease are of the fair-haired and blue-eyed type; the incidence is well known to be very low in the full-blooded Negro, and according to Askey (1944) it is also very low in Chinese and Japanese.

Hardgrove *et al.* (1944), studying 80 living cases of pernicious anemia in

patients of the dispensary type, found that a correct diagnosis had been made during the first year of illness in only 36 per cent of the cases, that in 53 per cent the diagnosis had not been made by the first physician consulted, and that in 86 per cent it was not adequately established until hospitalization occurred.

There was little significant advance in the treatment of pernicious anemia from the time that Addison described the disease in 1855 until Minot and Murphy, in 1926, announced that liver contains a principle which stimulates blood regeneration. These Harvard investigators, whose work was based directly upon the painstaking investigations of Whipple and his associates, who worked with dogs, found that a diet rich in liver was regularly followed by remission of the disease, without the employment of other therapeutic agents. They first reported 45 cases, but later brought the number up to 105 cases. Since that time the mortality rate for pernicious anemia has declined so uniformly in every age group that there cannot be the least doubt of the specific efficacy of the therapy. Full explanation for this magic is not yet at hand, but the classical studies of Castle and his associates have demonstrated almost beyond doubt that pernicious anemia is a deficiency disease conditioned by the lack of a specific intrinsic factor which is present in normal gastric juice but not in that of an individual with this disease. It is considered that the function of the intrinsic factor is to interact with an extrinsic factor supplied in the food to produce a hematopoietic substance active in preventing pernicious anemia in normal individuals and in checking its progress in ill individuals when given to them in some form derived from liver, kidney, or brain tissue, in which it is apparently stored. Meulengracht's (1939) work suggests, but by no means proves as yet, that the intrinsic factor may be secreted by the pyloric and Brunner's glands. Castle *et al.* (1944) believed it reasonable to regard the extrinsic factor as a thermostable component of the vitamin B complex as yet unidentified.

The practical discovery, made by Sturgis and Isaacs in 1929, that hog's stomach desiccated and defatted and taken by mouth can replace liver with equal effectiveness, has been borne out by the experience of physicians throughout the world. It is believed that the intrinsic substance postulated by Castle exists in an enzyme-like form in the stomach tissue and that it acts on the muscular coat while the stomach is being ground up in the fresh state, the stomach tissue here taking the place of Castle's extrinsic or food factor; the active principle thus formed is retained in the stomach preparation and, when swallowed, is rapidly absorbed and becomes at once available for use by the patient.

Miscellaneous Macrocytic (Pernicious) Anemias.—Israëls and Wilkinson (1936) described 4 cases of hyperchromic-megalocytic anemia characterized by normal or almost normal gastric acidity, little disturbance of the gastrointestinal tract, no involvement of the central nervous system, and lack of, or poor response to, anti-anemia therapy. To this syndrome, which they considered a new entity, they applied the title "achrestic anemia." Wauchope and Leslie-Smith (1938) reported a similar case, but it seems to me that much time and exhaustive study will be required to show that this separate classification is warranted. Schwartz and Legere (1943) reported a small series of atypical cases in most of which the symptomatology bore a striking similarity to that of subacute bacterial endocarditis; fortunately they did not set this up as a new subtype of pernicious anemia. Alsted (1939) reported

a patient subsisting on a near-starvation diet in which pernicious anemia is alleged to have arisen from lack of the extrinsic factor only; the patient of Townsend and Begor (1942), who lived on a protein-poor diet for twenty years, seems also to come in this class—indeed, Moore *et al.* (1944) felt that the macrocytic anemia occurring in some patients with pellagra or other vitamin B complex deficiency states is in many instances associated with a dietary deficiency of extrinsic factor plus poor absorption from the intestinal tract; they felt also, however, that inadequate production of intrinsic factor probably contributes to the forming of the picture. In the case of Fouts and Garber (1942), in a four-months-old infant whose mother had been on a meat-free diet during pregnancy, a macrocytic-hyperchromic anemia developed quickly after slight infection and decreased intake of food and responded rapidly to the daily administration of 0.25 U.S.P. units of purified liver extract; one of Bass's (1944) two extremely interesting cases closely paralleled that of Fouts and Garber except that there was no history of inadequate maternal diet during pregnancy, but the other was a case of a severely anemic allergic infant who was being fed goat's milk and who recovered when given a food containing protein in the form of amino acid; in Perkins' (1944) case of goat's milk anemia there was no response to the administration of iron, a corrected dietary or transfusion therapy, but the response to liver extract intramuscularly was dramatic. Adams and McQuarrie (1938) reported a severe functional anemia in a child, resembling pernicious anemia of adults and responding to liver therapy by complete and apparently permanent cure; 2 of Davis' (1944) 3 cases of a similar nature proved refractory to parenteral injections of liver extract but responded promptly to proteolyzed liver (not yet commercially available) administered orally.

Pernicious Anemia of Pregnancy.—Very rarely there occurs in pregnancy a type of anemia indistinguishable from classical pernicious anemia except that cord symptoms are not often seen and free hydrochloric acid is often present in the stomach. The response to liver therapy in these cases is frequently very slow and in many instances there is a complicating hypochromic anemia, so that iron as well as liver must be given. Davidson *et al.* (1942) reported a series of 16 cases of this type of exceptional severity, 6 of them continuing to be refractory to liver therapy for a month or longer; these authors proposed for the macrocytic anemia of pregnancy the term "megaloblastic anemia of pregnancy or the puerperium." The present consensus is that dietary deficiency underlies these anemias (though Wiener's, 1944, recent hypothetical association of this entity with erythroblastosis fetalis is extremely interesting). In a group of pregnant women in Philadelphia, in whom they deliberately maintained a deficiency in the members of the vitamin B complex, Elsom and Sample (1937) observed the occurrence of macrocytic anemias of moderate degree with some early evidences of cord involvement, but no consistent alterations in gastric acidity. The blood and clinical changes were corrected equally well by either liver extract intramuscularly or brewer's yeast by mouth (see also Tropical Macrocytic Anemia below). The results obtained by Watson and Castle (1945) in 3 cases indicated the desirability of a therapeutic trial of *orally administered* liver extract in these macrocytic anemias of pregnancy refractory to parenterally administered extract.

Tropical Macrocytic Anemia and Dimorphic Anemia.—Since 1930, Wills and her associates have been studying a very interesting type of anemia in

India. Morphologically it seems fairly closely to resemble addisonian pernicious anemia, but differs from the classical entity principally in not being associated with achlorhydria or increased serum bilirubin (indirect van den Bergh), and in manifesting no evidences of nervous system involvement. Previously thought to occur predominantly, if not exclusively, in late pregnancy, it is now believed to occur very frequently in males also, though pregnancy does seem to predispose to an attack; the late autumn and winter rise in incidence of cases is as yet unexplained. China, the west coast of Africa, and India are the principal areas of its endemicity apparently, but Trowell (1940–1943) reported such cases from East Africa, Fairley *et al.* (1938) from Macedonia, and the observations of Groen and Snapper (1937), and Rodriguez-Molina (1939), suggested that this entity may also be encountered in Holland and in Puerto Rico. All evidence points toward this being really a food deficiency disease, but whether the missing element is merely Castle's extrinsic factor is not altogether certain. The bone marrow responds to liver stimulation as in pernicious anemia, but Wills and Evans (1938) said that response is not obtained to the more highly purified extracts. Foy and Kondi (1939) found that the Macedonian cases do respond to purified extracts, but more recently Fairley (1940) has reported that the dose must be prohibitively high; Trowell (1943) also found high dosage necessary and, like Wills and Evans, preferred to use the crude extract. Therapeutic response is also obtained to an autolyzed liver extract known as marmite (vegex in the United States), with which cure can be obtained in very few cases of true pernicious anemia. Wills has shown that the active principle in this preparation is not any part of the vitamin B complex but is a substance which is water-soluble, heat-stable in acid medium, and not precipitated or inactivated by 80 per cent alcohol.

In some instances iron deficiency anemia and the type of macrocytic anemia under present discussion are both present and the resulting picture is a very confusing one; Trowell (1943) proposed the name "dimorphic anemia" for this combination. It is not at all unlikely that many instances of this type of anemia will be found on the Continent after the close of War II.

Sprue.—The typical anemia of sprue is of the macrocytic-hyperchromic "pernicious" sort and responds specifically to liver therapy; the matter is discussed in detail under Sprue.

Infestation with Diphyllobothrium Latum.—In some instances of infestation with the fish tapeworm there arises an anemia which closely resembles that of the true addisonian pernicious anemia in symptomatology except that complete achlorhydria is not invariable and marked spinal cord involvement is rare. Sometimes improvement or cure follows expulsion of the worm. This anemia responds fully to liver therapy; if I correctly interpret Castle and Minot (1936) they have strongly suspected these to be cases of true pernicious anemia incidental to, and somewhat modified by, the worm infestation (see Tapeworm for further discussion).

Anemia of Hepatic Disease.—Wintrobe's (1936) studies conclusively showed that in cases of hepatic disease, except when there is a complicating infection or loss of blood, the anemia is morphologically very similar to that of pernicious anemia. Achlorhydria is not the rule, however, nor are there often any evidences of cord damage. Wintrobe concluded that the anemia is very likely due solely to the inability of the liver to store the hematopoietic principle; the studies of Goldhamer *et al.* (1934), and of Rosenberg (1936)

support this hypothesis. This anemia due to hepatic damage may be controlled at times by the injection of liver extract.

Anemias Associated with Gastro-intestinal Pathology and Surgery.—There have been some reports of one or another form of chronic dysentery, and also ulcerative colitis, associated with anemias morphologically similar to the true pernicious type; injections of liver extract in these cases can be expected to make up for the decreased absorption of the marrow stimulant. Sturgis and Goldhamer (1939) listed also the following conditions which may be associated with an anemia of this type: total gastrectomy, extensive infiltrative carcinoma of the stomach, and various other intestinal lesions such as strictures and anastomoses; Barker and Hummel (1939) want to consider the anemia occurring in conjunction with strictures and anastomoses as a distinct disease entity.

ADMINISTRATION OF LIVER AND STOMACH PREPARATIONS

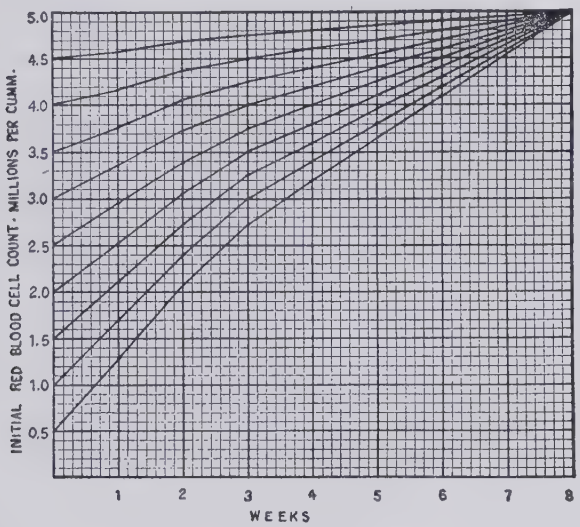
At the present time throughout the world intramuscular injection of liver extract has practically entirely replaced other methods of liver therapy for the following reasons: (1) Greater efficacy; patients in whom it is not possible to reach a completely normal erythrocyte count with oral methods of therapy can in most instances be brought up to normal by injection, since uneven and incomplete gastro-intestinal absorption does not condition the response. Likewise, in the presence of extensive liver damage with impaired storage capacity the injected extract is much more effective than that given by mouth. (2) Acceptability; as compared with the oral administration of liver or stomach preparations daily, the intramuscular injections three or four times weekly in the beginning and only once weekly, or even less often, thereafter, are greatly preferred by practically all patients. Since the freeing of the preparations from histamine, the anaphylactic shock type of reaction is now extremely rarely seen; the injection is usually not followed by excessive pain. (3) Travel; a patient can be intensively treated by injection before departing and then need not be concerned during weeks or months of sojourning where reliable supplies of the bulky preparations for oral administration, or fresh liver, may not be obtainable. (4) Cost; more hematopoietic principle can be had for the money when it is purchased as extract for injection, though of course patients who cannot learn to inject themselves after a while will necessarily have frequently to meet the physician's fee. (5) Speed; the patient in dire need in a severe relapse can be stimulated more quickly by injection than by oral administration in most instances.

Dosage of Liver Extract Intramuscularly.—This matter really comprises the three separate subjects which follow herewith:

Criteria for Guidance in Dosage.—There are no absolute ones really, since patients vary in response and the available commercial preparations are widely different in strength, with differences of as much as 2 cc. in dosage between them in order to obtain comparable results. The only safe plan is to use a reliable, clinically tested extract in dosage recommended by the manufacturer and to vary that dosage, especially not fearing to increase it, according to the reaction as indicated by frequent blood studies. Beginning two to ten days after therapy is started the reticulocytes rise to a major peak within three to ten days, the height of which peak is inversely proportional to the level of the red cells, other things being equal. The mature red cells require some time to begin reaching the peripheral blood stream

in full numbers, but usually in about two months the red cell count is within normal limits (Wintrobe, 1933: average for men, 5,400,000; for women, 4,800,000)—where it should be the aim of therapy to keep it thereafter. Riddle's (1940) study of the data on 523 patients indicated that neither the reticulocytes nor the erythrocyte response is superior for the purpose of estimating the effectiveness of treatment, but since the erythrocyte count is certainly the one most often employed, I am reproducing here with Dr. Raphael Isaacs' kind permission his chart of the erythrocyte response which may be expected in adequately treated cases.

A Dosage Plan.—The several leaders in the study of pernicious anemia have been employing the products of different manufacturers and hence their dosages have differed, but I think it will best serve the reader's purpose if I present here only the plan of one of these groups, namely Strauss and



The red blood cell count, at weekly intervals, for each initial red blood cell count after liver extract therapy, intramuscularly. Example: With an initial red blood cell count of 1 million per cubic millimeter the count at the end of one week will be 1.7 million, at two weeks 2.4 million, at fifteen days 2.5 million, and so on.

his associates in Boston, who have for many years been employing the Solution Liver Extract Crude-Lilly in the strength which contains 1 U.S.P. unit to the cubic centimeter. This extract, not being highly purified, contains many other substances present in liver besides the hematopoietically active material for pernicious anemia and is preferred by many men for this reason, the feeling being that such crude extracts are especially effective against the neurological involvements. In commencing the management of a previously untreated patient, Strauss *et al.* inject 10 cc. every three or four days during the first two or three weeks; thereafter weekly injections of the same amount are given for the remainder of the first year. If the results have been satisfactory with regard to every aspect of the disease during the year, they feel that the 10 cc. injections may then be given once in only two weeks, adequate maintenance requiring the injection of a dose at intervals of one to four weeks depending on the individual case. Weekly dosage must be at

once resumed upon the reappearance of any manifestation of the disease. They have had cases in which more than 20 cc. weekly were necessary to arrest the progress of spinal cord lesions; especially resistant are cases complicated by infection or arteriosclerosis.

Massive Dosage.—Miller (1936) sought to determine whether patients can store, and use as their needs require, the potent hematopoietic substance if given in massive amounts during a short period of time. It seemed from the results in his 4 patients that the method might prove feasible—if it should it would of course be a boon in selected cases such as of persons obliged to travel in remote districts for protracted periods. However, Strauss and Pohle (1940) concluded as the result of treating each of 12 patients in relapse with 160 cc. of Solution Liver Extract Crude-Lilly intramuscularly during a period of one week that the majority of patients cannot be satisfactorily treated by the use of massive injections at long intervals. Askey (1941), upon the other hand, found that the use of an initial large dose of 10 to 20 cc. of Solution Liver Extract Purified-Lilly ("purified" extracts contain 5, 10, or 15 units per cc. against 1 or 2 units per cc. for the "crude") enabled him to obtain satisfactory control in 16 of 19 patients who were thereafter given maintenance injections at only monthly intervals. Schwartz and Legere (1944) felt, as a result of 88 relapses due to self-neglect in 54 individuals, that accurate evaluation of the results of massive dose therapy is unlikely because of the difficulty of making sufficient adjustment for the highly individualized behavior of patients with pernicious anemia during remissions.

Reactions to Intramuscular Liver Injections.—One might almost say that systemic reactions to these intramuscular injections do not occur, yet very occasionally a patient does develop peripheral circulatory collapse very suddenly and apparently unaccountably, though Reznikoff (1940) reported one instance in their clinic in which they were reasonably certain that the material had entered a small blood vessel. Asthmatic, urticarial, gastrointestinal and other allergic reactions are being increasingly reported but the number is still not very great. According to Feinberg *et al.* (1943) cutaneous and intracutaneous tests indicate that the specificity of this reaction is related to a special fraction of liver not bound with the ordinary protein fraction but associated with the antianemic fraction. Changing the brand of liver extract will sometimes suffice to eliminate these reactions. Taylor and Hilger (1941) reported that in 2 patients the oral administration of 50 to 60 units of histaminase daily for two days before and on the day of injection completely prevented the systemic reactions to the parenterally administered liver extract. Delikat (1943) reported desensitization in one case in which the beginning dose was 0.1 cc. which was increased by the same quantity at each successive dose given every second day until a dose of 1 cc. was reached; thereafter an increment of 0.2 cc. was used; after reaching 3 cc. the dose was increased by 0.5 cc. at two weekly intervals until 4 cc. could be given in a single injection, the patient thereafter tolerating this dose every four to five weeks. Another of Delikat's patients attended the clinic every six weeks and received her requirement of liver extract in divided doses starting with 0.1 cc. with increments of 0.1 cc. at intervals of twenty minutes until the first signs of intolerance appeared; after the slight reaction passed away she went home and returned on the following day at which time dosage was started at the level reached on the previous day and proceeded at increments of 0.2 cc. at twenty-minute intervals; in this patient

the full requirement of 4 cc. for six weeks was usually injected thus in two days. Of course when none of these methods succeeds these patients have to be treated by liver or stomach preparations by mouth.

Results of Liver Extract Therapy.—It is simplest to consider this subject under the following heads:

Objective Changes.—Usually the skin begins to acquire color in the first week and later becomes healthy and moist in appearance. The mucous membranes share in this improvement and the tongue returns to normal in most instances; persistent tongue lesions are felt by some observers to be associated with marked cord involvement. Isaacs, Sturgis and Smith advise painting the lesions with 1 to 2 per cent silver nitrate. Hemic murmurs, anginal symptoms, spleen palpability and edema disappear; though it should be remarked that if the patient has much cord involvement and has been bedridden, dependent edema may become more marked as he becomes ambulant. Some patients respond with a polycythemia, so that for awhile they will have a very red appearance and a blood count above normal.

Subjective Changes.—The improvement in state of mind is usually rapid and marked. Appetite, physical strength and sexual power return. The distressing gastro-intestinal symptoms disappear, though if there has been normal bowel activity looseness may supervene for a short time. Dizziness, blurred vision, headache, dyspnea disappear.

Effect on the Neurologic Manifestations.—The effect of specific therapy upon spinal cord lesions is a point about which there has been considerable controversy and there is currently building up some opinion to the effect that the neural changes arise from a deficiency of some unidentified factor other than that required for hematopoiesis. Nevertheless I think there is a preponderance of opinion favorable to the belief expressed by Strauss *et al.* (1940), of the Boston group, that adequate therapy is effective in preventing further spinal cord damage in patients who already have fairly marked lesions and in preventing the development or unfavorable progression of lesions in patients with no or minimal damage. This opinion was based upon their experience over an average period of seven years in 21 patients with advanced lesions and 64 with little or no neurologic disturbance at the beginning of treatment. These workers recognize that apparent improvement in the neurologic condition may be entirely due to betterment of general health and strength, reeducation and training, and improved circulation and subsidence of edema in the spinal cord; furthermore, that since peripheral nerves are capable of complete regeneration as long as the cell body has not degenerated, signs and symptoms referable to such peripheral nerve injury may completely disappear and lead to the impression that marked regeneration has occurred in the spinal cord. But they apparently feel that failure to check progression of a cord lesion can be blamed in any given case upon one or a combination of the following points: (*a*) that concomitant septic states—urinary tract infections secondary to "cord bladders," bed sores, etc.—much reduce the effectiveness of liver therapy; (*b*) that many reported failures are due to lack of realization that there is no more a "standard" liver dosage in pernicious anemia than there is a standard insulin dosage in diabetes mellitus; (*c*) that too few cases are treated long enough before they are reported as failures.

Effect on Childbearing.—Pregnancy used to be looked upon as a calamity in the life of a woman with pernicious anemia, but women are now carried through safely to the birth of healthy babies.

Effect on the Dangers of Surgery.—Apparently patients on liver therapy tolerate operations very well upon the whole and are good surgical risks, but Hahn (1934), reviewing 32 cases, stated his strong impression that surgical procedures definitely tend to precipitate or increase neurologic symptoms; he recommended intensification of treatment both before and after operation.

Effect on the Gastric Acidity.—A few cases have been reported in which there was a return of free hydrochloric acid after adequate liver therapy, but Goldhamer (1937), reviewing the subject, doubted that these were cases of true pernicious anemia. He did find, however, that the intrinsic factor is present in the gastric juice in induced remission.

Liver Extract by Intravenous Injection.—There are preparations available for intravenous injection but their advantages over the intramuscular preparations are certainly doubtful (see, however, Sprue). Severe reactions, with chill, fever, nausea and vomiting, occur very often; such preparations had best not be given at all to patients with an allergic history. Sturgis makes the point that allergic reactions to intramuscular injections are much more likely to occur if the patient has previously been injected by the intravenous route. The Council does not accept liver extracts for intravenous administration.

Liver Extracts and Hog Stomach Preparations for Oral Administration.—These preparations may be added to milk, cereals, tomato, or fruit juices, or they may be given as a thick purée or in soups (heated to taste but not boiled); they may be eaten with or between meals, the entire amount at one time or in several portions throughout the day. The Council-accepted (1944) preparations are the following, the dosage being the amount required to supply one U.S.P. oral unit per day: Solution Liver Extract-Armour, 45 cc.; Solution Liver Extract Oral-Lederle, 60 cc.; Liver Liquid Extract Oral-Upjohn, 45 cc.; Liquid Extract of Liver-Valentine, 45 cc.; Capsules Liver Extract Concentrate-Armour, 9 capsules; Liver Extract Powder-Lilly, 3 vials; Liver Extract Powder-Parke-Davis, 6 vials; Pulvules Extralin-Lilly (Liver-Stomach Concentrate), 12 pulvules; Ventriculin-Parke-Davis (Liver-Stomach Concentrate), 40 gm.

Fresh Liver by Mouth.—It is now generally agreed that the amount of fresh liver required to induce remission and maintain health in the average adult uncomplicated case of pernicious anemia is 200 to 400 Gm. (approximately ½ to 1 pound) net weight daily. It may be taken either raw or lightly cooked, provided the water employed in cooking is added to the completed dish, for the active principle is soluble. Many recipes have been made available but most patients tire in time of all of them. Falconer (1931) has described his own experience in taking raw liver in large cachets—an easy method which does away with the trouble of "lightly" cooking and also makes it possible to use the tough, fibrous, and hence cheaper cow's liver. The cachets must be filled just before using else they become soggy and liable to come apart in the mouth. Kidneys are about one-half, sweetbreads and brains about one-third as valuable in treatment as liver. The liver may be eaten at one or be divided between all the meals of the day. Farquharson and Graham (1930) found a broth made from beef or pork liver to be inexpensive, palatable and effective in treatment. It is made as follows: 500 Gm. of liver are finely ground in a meat chopper, care being taken to save all the juice. Two glasses of water are added, and it is transferred to a fruit jar, shaken for a moment and allowed to stand for eight to twenty-four hours, if possible in a refrigerator. Finally it is heated to the boiling point, and after cooling

sufficiently is strained through cheesecloth. By twisting round and round, as much fluid is expressed as possible and the total amount of fluid obtained is given to the patient every day. It may be taken cold or hot, and various flavoring agents—onions, soup powders, tomatoes—may be added if desired. Davis *et al.* (1943) described a method for the production of a palatable and readily assimilable whole-liver preparation by means of enzyme digestion of raw liver with papain; but the process was too laborious and complex for employment in the home and a preparation of this "proteolysed liver" is not as yet commercially available.

Resistance to Liver Therapy.—In their original paper, Minot and Murphy indicated that infection could inhibit the effectiveness of the therapy, an observation which has been substantiated in many subsequent reports. However, we cannot yet be certain that resistance to liver therapy may not very occasionally be encountered, for a few cases have been reported in which there was progression to a typical pernicious anemia fatal termination in the absence of infection and under adequate therapy. It is a fact worthy of note that since parenteral liver extracts have come into general use no such reports of failure have appeared in the literature—at least I have seen none.

OTHER THERAPEUTIC MEASURES

Brewer's Yeast.—Wintrobe (1939) reported the employment of brewer's yeast in daily dosage of 1 to 2 Gm. per kilogram of body weight with variable but in some instances quite satisfactory results in a small series of cases; he made his report, however, primarily as a contribution toward further understanding of the antipernicious anemia factor rather than with the object of proposing a new type of therapy. Heinle and Miller (1939) also tried yeast in 2 patients but did not obtain as good responses as could be had with ventriculin or with the intramuscular injection of liver extract.

Vitamins.—Hansen-Pruss (1938) failed in his attempt to affect the course of 3 patients whom he gave full doses of *nicotinic acid* (*niacin*). Zillhardt *et al.* (1941) thought that the administration of *thiamine hydrochloride*, provided it was given intramuscularly in 10 mg. dosage three times weekly, had a beneficial effect on the residual neural signs and symptoms that persisted in spite of intensive antipernicious anemia therapy; but their series of cases was very small and I have seen no subsequent reports. Dyke *et al.* (1942), studying patients on a restricted dietary in England during War II, reported three cases in which large doses of vitamin C (*ascorbic acid*) permitted a response to liver extract therapy otherwise unattainable. They further said that applying this treatment to a larger number of patients it was found that after a month's course of 100 mg. of ascorbic acid daily there was in every case an increase of up to 1,000,000 red cells per cubic millimeter with corresponding improvement in the general health and without any increase in their maintenance dose of liver extract. These findings with regard to vitamin C will certainly require confirmation before they are generally accepted.

Transfusion.—Prior to the institution of liver treatment, undoubtedly the transfusion of whole blood produced better and more permanent results than any other therapeutic measure. Transfusion is by no means a cure but it has certainly brought many a moribund patient back to life, and in some cases it has probably been responsible for the occurrence of a remission. Such cases as do respond with a remission may require anywhere from 5 to 15

transfusions before a normal blood count is approached. The utmost extension of active life attainable by the use of this measure probably follows upon transfusion of 350 to 450 cc. at intervals of three to five days instead of giving larger transfusions at longer intervals. A number of observers still feel that the transfusion of about 500 cc. of blood is the most valuable of all emergency measures to effect relief from the anoxemia which is involving every organ in the body. Others feel that since serious transfusion reactions occur with notorious frequency in individuals with pernicious anemia this danger should always be weighed against employment of the measure if a liver preparation suitable for injection is available; however, an occasional patient will undoubtedly die under these circumstances before sufficient time has elapsed for a response to liver therapy.

Since 1940 the use of red cell residues that are by-products of plasma production, resuspended up to the original volume in physiologic saline, has been increasingly practiced; in 1944, Cooksey and Horwitz were able to report on 15,000 such transfusions in the city of Detroit alone. Among recent reports that I have seen those of Murray *et al.* (1943), Alt *et al.* (1944), and Cooksey and Horwitz (1944) specifically mention the use of red cell transfusions satisfactorily in pernicious anemia. Since there is practically universal testimony to a lowered incidence of transfusion reactions when red cell suspensions are employed instead of whole blood, I should think that this new method would be highly advantageous.

Iron, Arsenic and Hydrochloric Acid.—It is believed that in pernicious anemia the breakdown products of the red cells are stored in the body and are available at once for the manufacture of hemoglobin should normal blood formation occur as the result of a natural remission or of treatment with one of the new specifics. However, in a few cases the amount stored may not be sufficiently great to prevent the color index from falling to and remaining below 1.0 for a considerable period as the red cells continue to rise. Under such circumstances iron is indicated (Sturgis, 1936); undoubtedly there are instances in which neither the blood count nor the hemoglobin level can be pushed up to normal without the use of the metal, but these cases are certainly not frequently encountered. The routine employment of iron in pernicious anemia is unjustified.

It is generally agreed today that arsenic no longer has any place in the treatment of pernicious anemia.

Since the overthrow of the intestinal contamination theory of the etiology of pernicious anemia by the newer studies which have shown the disease to belong among the disorders of deficiency, there seems little rationale for the employment of hydrochloric acid. However, a number of physicians continue to prescribe it in doses of $\frac{1}{2}$ to 2 drachms (2–8 cc.), well diluted and taken as a routine with meals, finding that flatulence and diarrhea that are not alleviated by specific therapy are kept well in check by the addition of this measure.

ANEMIAS PRIMARILY BENEFITED BY CORRECTING AN UNDERLYING DEFICIENCY

Vitamin Deficiencies.—Anemia does not characteristically occur in the states due to vitamin deficiency of one sort or another, and when seen it is

nearly always of the hypochromic-microcytic type caused by insufficient intake of iron, and is correctable by the administration of iron together with the vitamin which has been ingested in insufficient quantity. A rather constant exception, however, is scurvy, in which anemia is so regularly seen as practically to constitute one of the invariable signs. It is usually of the hypochromic type but may occasionally resemble the pernicious group at least in its morphologic characteristics, achylia and cord symptoms of course not being present. This anemia is rapidly corrected by the administration of vitamin C according to any of the methods discussed under Scurvy—at least Parsons (1933) says that it is, Castle and Minot (1936) say that it is, and the work of Mettier, Minot and Townsend (1930) seemed to leave little doubt about the matter. Josephs (1936), however, very surprisingly took the position that in infants in the majority of instances the anemia is not affected by supplying the vitamin but is promptly cured by the administration of iron. In the adult patients of Mettier *et al.* neither large doses of iron nor liver were able to accomplish the results easily achieved with vitamin C. In using iron in scurvy, Parsons warned against accompanying it with copper, which he said would destroy the vitamin.

The macrocytic anemia of pellagra is discussed under the miscellaneous macrocytic anemias in the section on Anemias Primarily Benefited by Liver-Stomach Therapy.

Thyroid Deficiency.—Anemia is a not infrequent finding in cretinism and myxedema, though it is not actually demonstrable so often as the pallor would lead one to expect. Usually of the hypochromic (iron deficiency) type, it may also at times have hyperchromic (pernicious) characteristics; particularly is the latter true in myxedematous individuals in whom, according to Lerman and Means (1932), the incidence of achlorhydria is high. Both iron and liver, depending upon which is indicated by the morphologic characteristics of the anemia, will induce bone marrow responses in these cases, but it seems undeniable that thyroid substance alone will slowly accomplish the same thing. Supplementing thyroid administration with one or other of the hematopoietic agents therefore seems the ideal therapy. In an elderly man with chronic untreated myxedema and an associated hyperchromic macrocytic anemia in whom four months of treatment with thyroid, liver extract and iron apparently did not influence the anemia, Glass (1943) reported that he obtained prompt and complete erythropoietic response when testosterone was used in addition.

ANEMIAS PRIMARILY BENEFITED BY COMBATING BLOOD LOSS

This matter is treated as one of the types of iron-deficiency anemia in the earlier part of this chapter.

ANEMIAS PRIMARILY BENEFITED BY COMBATING THE UNDERLYING INFECTIONS

In sepsis, which is the most frequent cause of severe acute anemia of infectious origin in the temperate zones, transfusion is not often employed

in these days of specific chemotherapy. Malarial anemia, whether severe or not, is most effectively combated by use of the specific antimalarial drugs. Treatment of the very serious anemia of blackwater fever is discussed in the article on that disease. Occasionally malaria—and syphilis also, but the other infectious diseases more rarely—is followed by the acquired type of chronic hemolytic jaundice, in these instances curing the infection does not always cure the anemia. Anemia often results from the paroxysmal hemoglobinuria which occurs occasionally in syphilis; specific antisyphilitic treatment may not entirely abolish the *in vitro* evidences of hemolysis, according to Castle and Minot (1936), but it usually causes disappearance of the clinical manifestations.

In states of chronic infection, most notably in tuberculosis and in the rheumatic and focal infections, a "low-grade" microcytic and slightly hypochromic anemia often appears; occasionally there are evidences of bone marrow depression. Administration of iron under these conditions is a time-honored custom, but I know of no controlled study of its worth before the termination of the infection. Liver-stomach preparations are almost certainly of no value.

ANEMIAS PRIMARILY BENEFITED BY COMBATING CHEMICAL POISONING

A few chemical substances administered as drugs, and a larger number with which many individuals are obliged to come into contact in this industrial age, are capable of considerably depressing the hematopoietic system. Those which are of principal concern to the man in general practice are discussed elsewhere in the book (see the chapter on Poisoning, and the Index); for a consideration of the others the reader will be obliged to consult specialized works on industrial toxicology.

ANEMIAS PRIMARILY BENEFITED BY SPLENECTOMY

Congenital hemolytic anemia (icterus) is the classical entity in which splenectomy almost invariably arrests progress. The disease occurs on a familial background of the same malady and is characterized by relatively mild jaundice (which is accentuated at times of increased hemolysis), by enlargement of the spleen, chronic anemia with many erythrocytes that are microcytic and spheroidal, reticulocytosis out of proportion to the reduction in erythrocytes, increased fragility of the erythrocytes in hypotonic saline solutions, and increased urobilin in the blood. In the presence of this typical picture, splenectomy will apparently quickly and permanently put a stop to the hemolysis, though the spheroidicity of the cells persists. Whether the concept of an acquired form of hemolytic anemia of this type is admissible is at present controversial. Many observers feel that such cases are really only latent stages of the congenital disease which are diagnosed when they have become activated by some infectious, toxic, or metabolic disturbance. In a recent discussion in which he championed the acquired form as a separate

entity, Fowler (1941) nevertheless pointed out that a diagnosis of this form is not infrequently made embarrassing by the subsequent appearance of case histories or of active cases in the patient's family. The especially interested reader will likely find the review of Dameshek and Schwartz (1940) very stimulating. Of the 106 cases reported in the literature at the time they wrote, transfusions were given in 66 and were unsuccessful in arresting the disease in 22 instances; splenectomy induced arrest in 20 of the 23 cases in which it was performed. A recent very interesting case reported by Dameshek and Levine (1943) indicated that repeated transfusions in cases of acute hemolytic anemia may be followed by isoimmunization and the development of irreversible hemolysis; as a result of this, splenectomy—which might originally have been curative—may prove ineffective. Dameshek and Schwartz considered Lederer's anemia as almost certainly the same thing as acute hemolytic anemia, and most hematologists seem now to be in agreement that this is so.

ANEMIAS PRIMARILY BENEFITED BY TRANSFUSION WITH Rh NEGATIVE BLOOD

(*Erythroblastosis Fetalis and Certain Transfusion Reactions*)

In 1940, Landsteiner and Wiener discovered the existence in man of a new blood group factor, designated the Rh factor, which is inherited as a Mendelian dominant just as are the previously well-known factors A, B, AB and O. Since the original discovery the further studies of Wiener and his associates have shown that there are eight theoretically possible subtypes of the Rh factor, all save one of which have already been actually encountered; but the fact of chief clinical importance is that there is a certain small proportion of individuals who do not have this Rh factor in their blood—about 13 per cent of whites are Rh−, perhaps a slightly smaller proportion of Negroes and less than 1 per cent of Chinese and Japanese. The significance of Rh negativity may be expressed as follows: (*a*) the Rh factor exists in the red blood cells of Rh+ persons and is an antigenic substance; (*b*) the blood does not contain agglutinins (antibodies) against this Rh factor; (*c*) when the blood of an Rh+ person is introduced into the circulation of an Rh− person, agglutinins (antibodies) against the Rh factor will be developed in the blood of the Rh− person; (*d*) if, then, upon a subsequent occasion the Rh− person again is the recipient of Rh+ blood there will occur a violent reaction between this blood and the agglutinins which have been built up in the Rh− blood by the preceding administration of Rh+ blood. Kracke and Platt (1944) very graphically presented the possibilities of Rh reactions in the terms of 4 typical cases seen by them at the Emory University Hospital. *Case 1* was a two-day old infant of an Rh+ father and an Rh− mother. The father had transmitted the Rh+ factor to the fetus, the fetus had passed it as an antigen through the placenta to the mother who had developed antibodies against it in her blood, and these antibodies returning to the fetus destroyed its red blood cells. The child had typical erythroblastosis fetalis. *Case 2* was that of a twenty-five-year-old primipara who was delivered of a normal infant but who was given a blood transfusion because of severe hemorrhage as the result of a lateral rupture of the placenta sustained during

delivery. She experienced an immediate severe reaction and examination of her blood revealed that she was Rh−. In this case her Rh+ infant had immunized her against Rh+ blood but for some reason her antibodies had not traveled back through the placenta to the infant; the infant therefore escaped erythroblastosis fetalis but when the mother was subsequently given the transfusion of Rh+ blood she herself experienced the reaction. *Case 3* was that of a fifty-eight-year-old patient with an established diagnosis of aplastic anemia. She had received numerous transfusions before entering the hospital, but careful questioning elicited that the first two transfusions were uneventful while each succeeding one had produced a more severe reaction. This patient was found to be Rh− and demonstrated the production of anti-Rh agglutinins in an Rh− patient by means of multiple transfusions of Rh+ blood. *Case 4* was that of a forty-year-old female admitted eight months postpartum with a diagnosis of Banti's syndrome. It was decided to remove the spleen and by way of preparation for the operation to give her two or more blood transfusions; but because of her recent pregnancy it was decided to test her for Rh factor. She was found to be Rh− and in addition to have a quite enormously high titer of anti-Rh agglutinins in her blood, which presumably resulted from her last pregnancy. This case presented an example of the value of prophylactic measures to avoid transfusion reactions, for such a reaction would surely have occurred had this patient been transfused with Rh+ blood. The experience of Young and Kariher (1945) with 2 patients indicated that sensitivity to the Rh factor, once it is acquired, may persist for many years and probably for life; in their cases they proved retention of sensitivity nearly eight and sixteen years respectively after the last immunization by pregnancy.

Levine's (1944) studies indicated that an Rh− person who has been immunized against Rh factor in one or another manner exemplified in the case reports above remains immunized for many years if not permanently. As time goes on we shall very probably find that a large proportion of hemolytic transfusion reactions which have heretofore been baffling mysteries will be explainable upon the basis of this new Rh factor concept, but it is not superficially apparent why the incidence of erythroblastosis should be only about 0.1 to 0.2 per cent of births. The following reasons have been proposed by investigators in this field, some of them substantiated by actual findings and others mere speculation: (*a*) variations in the permeability of the placenta may effect the passage of Rh+ factor and anti-Rh agglutinins between mother and fetus; (*b*) more than one pregnancy may often be required to induce an adequate degree of immunization of the mother, the modern tendency to restrict the number of children therefore working against a high incidence of erythroblastosis; (*c*) mild and unrecognized forms of the disease may occur; (*d*) heterozygous fathers, *i.e.*, those who have inherited the Rh factor from only one parent, transmit the factor to only some of their children and of course the children who do not inherit it escape erythroblastosis. Potter (1944) described twins one of whom died of erythroblastosis and the other remained normal, the affected twin and the father being Rh+ and the normal twin and the mother Rh−. She contended that the father was heterozygous for the Rh factor and that two ova were fertilized, one by a sperm carrying an Rh+ gene and the other by a sperm carrying an Rh−. The mother had been sensitized to the Rh factor either in a previous pregnancy when an Rh+ fetus had been carried or possibly during the course of this

pregnancy by the Rh+ twin. The antibodies produced in the mother passed through the placentas of both fetuses but affected only the one which was Rh+. The study of Race *et al.* (1943) showed that about 57 per cent of Rh+ males are heterozygous.

THERAPY

The only matter to be considered in therapy is how to transfuse Rh− persons in any of the above described categories or in infants with erythroblastosis fetalis. Of course blood of the patient's own group should be used, or of group O when tests have not been made, and it should be Rh− blood. In Rh− individuals who have become immunized to Rh+ blood the imperative necessity for the use of Rh− blood only is of course obvious. The necessity for the use of Rh− blood in infants with erythroblastosis fetalis who are practically all Rh+ is not quite so clear, though Rh− blood as a matter of fact is always used because of the possibility of free anti-Rh agglutinins being present in the blood streams of such infants. The largest series of erythroblastotic infants so treated that has come to my attention is that of Race *et al.* (1943) 18 of whose 19 consecutive patients were transfused with Rh− blood, all acquiring a normal blood picture with at most two such transfusions; these workers recommended relatively large transfusion as no hemolytic reaction is to be feared and the general condition of the infant is thus very rapidly improved. Potter *et al.* (1943), however, said that they have not observed nor have they been able to find a record of the demonstration of anti-Rh agglutinins in the blood of infants with erythroblastosis fetalis, and since these infants are Rh+ they raised the question whether it might always be necessary to employ Rh− blood in them. Wiener (1944) stated that in erythroblastosis fetalis the mother's washed cells are always suitable for transfusion therapy of the infant because the agglutinins against Rh+ cells are washed away in the plasma. On the basis of the demonstration by Witebsky *et al.* (1942) of Rh antibody in breast milk, it would seem inadvisable to permit mothers of infants with erythroblastosis fetalis to supply these infants with breast milk.

ANEMIAS FOR WHICH THERE IS NO SATISFACTORY THERAPY

This category embraces the anemias for which no place can be found anywhere in the therapeutic classification which I have been employing in this chapter. In the hemolytic entities among them, transfusion sometimes tides the patient over until hemolysis ceases spontaneously; otherwise they really cannot be effectively treated in the present state of our knowledge. The list is short: aplastic anemia; Banti's disease (the advisability and value of splenectomy are controversial points); Cooley's anemia (familial erythroblastic anemia, target cell anemia, thalassanemia, Mediterranean Disease—the reviews of Smith, 1943, and Dameshek, 1943, are most interesting); leuko-erythroblastic anemia; sickle-cell anemia; anemia of toxic nephritis (see Nephritis); anemias resulting from radium or roentgen ray injury; anemia in the leukemias, Hodgkin's disease, and carcinomatosis of the bones; anemias of Albers-Schönberg's, Machiafava-Michelis, Gaucher's, Niemann-Pick's, and Schüller-Christian's diseases.

BLOOD DISTURBANCES OTHER THAN THE ANEMIAS

ERYTHREMIA

(*Polycythemia Rubra Vera*)

Erythremia is a rare disease occurring in all races, in either sex, and usually after the age of fifty. The cause is unknown but in some of the cases, usually the milder ones, there is a distinct familial background. The patient complains of lassitude, weakness, loss of weight, dizziness, tinnitus, congestive sensations especially in the hands, dyspnea, gastro-intestinal disturbances, and often severe headache, muscular spasms and neuralgias and paresthesias of the extremities. There is a pronounced hemorrhagic tendency in the disease. Examination reveals red cyanosis of the face and hands (though it is said that an occasional patient may be actually pale, but it is doubtful if any victim of this disease is at *all* times pale), a greatly enlarged spleen in the majority of instances, congested conjunctivae and a typical blood picture. The red cells are increased to from 8,000,000 to 14,000,000; there are a great many immature cells present and differences in staining are marked; the number of white cells is usually two or three times the normal and the platelets are also sometimes much increased; hemoglobin is more than 100 per cent. Although the total blood volume is greatly enlarged, the increase in plasma is not in direct proportion to that in cells, with the result that viscosity is much increased. Despite the diffuse capillary dilatation that is known to occur in this disease, it is quite surprising that the heart rate is not greatly increased and the organ itself hypertrophied more often than is actually the case. Kidney function is often impaired and both blood pressure and the basal metabolic rate sometimes increased.

Dameshek and Henstell (1940) felt that erythremia is probably more common, particularly among Jews, than is ordinarily suspected, and that it may masquerade for months or years under such guises as neurasthenia, migraine, cardiovascular-renal disease, gastro-intestinal disorders and peripheral vascular disease. An increased excretion of uric acid in the urine is said to be frequently associated with polycythemia vera. Tinney *et al.*, reporting in 1943 and again in 1945, described 8 cases in which both polycythemia and gout were present; they also said that neurologic symptoms were presented in 78 per cent of 163 cases at the Mayo Clinic and that in 55 of these cases the patients came to the Clinic primarily because of their neurologic complaints. Carpenter *et al.* (1943) reported two cases in association with cerebellar hemangioblastomata, both cases apparently recovering upon the removal of the neoplasm. This is a fatal malady but there are remissions in most cases. Death seldom occurs under five years and may be deferred as long as twenty years, though this is unusual; some of the cases of long standing seem to merge into anemic, leukemic, or thrombocytopenic states. If death is directly attributable to the erythremia, it is consequent upon increased sluggishness of the circulation or due to a vascular catastrophe, such as hemorrhage or thrombosis.

THERAPY

Phenylhydrazine Hydrochloride.—In 1924, Owen reported a case in which he had successfully used this drug, and in 1925 he brought the number of cases up to 5. These patients were all benefited, as was evidenced by a uniform decrease of the hemoglobin and red cells, a great improvement in all the symptoms, and a reduction in blood pressure of the three individuals who had hypertension. Since that time a large number of case reports has appeared in the literature, in most of which the drug had been used very successfully. The dosage plan advocated by Owen is the one usually followed: (*a*) treatment may be safely begun in most instances with 3 grains (0.2 Gm.) daily for three or four days, then $1\frac{1}{2}$ grains (0.1 Gm.) daily until the leukocytes increase in number or the hemoglobin falls below 100 per cent; (*b*) with the advent of either of these two occurrences, usually after several weeks, the $1\frac{1}{2}$-grain dose may be given every second or third day, or the drug may be stopped altogether, resuming medication when the hemoglobin and red cells rise or the leukocytes begin to fall; (*c*) gradually the interval between doses can be lengthened with the hope of ultimately maintaining the blood count within normal limits on $1\frac{1}{2}$ grains once a week. However, the experimental studies of Griffin and Allen some years ago indicated that the leukocytosis cannot always be taken as a reliable index for therapy since the increase in the white cell count may be at times predominantly due to the breaking down of red cells and at other times to stimulation of the hematopoietic system; it very doubtfully indicates damage to liver cells. In Stealy and Sumerlin's (1944) valuable experience of eleven years' medication of 1 patient, they several times felt justified in continuing with the drug through a period of extreme leukocytosis unaccompanied by much decrease in the red cell count. Their dosage was a total of 2.1 Gm. (about 32 grains) of the drug divided into daily doses of 0.1 Gm. ($1\frac{1}{2}$ grains) each; after each such dosing period there was an interval of one and one-half months without drug treatment. Instances of acquired tolerance to the drug, requiring increase in dosage, have been reported, but in Stealy's (1932) experience such periods of tolerance were always temporary.

It has been suspected that injury to the liver or kidneys might result either from the drug itself or from excess hemolysis, but clear-cut proof of this has not been forthcoming. Stealy and Sumerlin's (1944) patient, treated for eleven years, revealed extensive liver damage upon autopsy six years later, but since evidences of this liver damage were not observed until the last year of life it was felt that it was not possible to say conclusively whether the drug was the cause of the liver involvement. Certainly one should carefully watch these patients and not gauge the use of the drug merely upon the evidence that through it such symptoms as pain in an extremity are being relieved. Kennedy (1934) gave his patient 4 short courses of treatment without untoward effect, but the fifth produced a severe hemolytic crisis, which he successfully combated by blood transfusion and the administration of liver extract. Giffin and Conner felt, from a review of the literature several years ago and their own experience, that (*a*) patients should be kept ambulatory as much as possible; (*b*) advanced cases confined to bed should not receive the drug; and (*c*) it should be given with greatest possible caution to those above sixty years of age, to patients with marked arteriosclerosis and to those who manifest evidence of thrombosis or advanced visceral injury.

Acetylphenylhydrazine.—Stone *et al.* (1933) used this drug satisfactorily

in 2 cases over periods of seven and four and one-half years, respectively, and believed it to be superior to the above preparation because it is probably less toxic and the dosage is easier to regulate. The drug seems now to have become generally the one of choice. McAlpin and Smith (1938) treated 14 cases, starting their patients on $1\frac{1}{2}$ grains (0.1 Gm.) daily for two or three days, then allowing a few days' rest, doing a blood count, and then starting over again. When necessary after three or four weeks of this treatment the dose was gradually increased to 4, 5, or rarely 6 doses per week. If there was *any* drop in erythrocytes and hemoglobin the drug was stopped at once for a week or more until regeneration to a safe level occurred. The attempt must of course be made to find the individual tolerance of each patient, but this is far from a simple thing to do because there seems to be a cumulative effect difficult to estimate. Reznikoff (1940) said that some patients can be kept with a fairly normal blood count for a long period on only 0.1 Gm. once a week while others will require that amount every other day. In addition to a sudden drop in the red cell count, McAlpin and Smith listed the following as signs of overaction of the drug; jaundice, gastro-intestinal symptoms and fever (which alone acted as a danger signal in one of their cases).

Potassium Arsenite.—Forkner, Scott and Wu (1933) obtained distinct improvement in all of their 6 patients by saturating with Fowler's solution in the conventional way except that they liked to reach 20 minims (1.2 cc.) three times daily instead of stopping at 10 minims as is usual in other conditions.

Roentgen Therapy.—Irradiation of the spleen is contraindicated since there are a number of cases on record in which the procedure has increased the severity of the disease; irradiation of the long bones, however, seems to be of some value, improvement taking place in most cases. The usual practice is to apply a rather large dose to the long bones, the scapula, the sternum, the pelvis, and eventually the vertebral column, or the ribs. The effect is temporary, and Minot has said that as time goes on the therapy often becomes ineffective. A considerable, or even a sudden inconsiderable, decrease in the leukocytes of the circulating blood indicates that the leukocyte-forming tissue of the bone marrow is being injured and calls for immediate cessation of the treatment. Hunter (1936), following the earlier European observers, believed general irradiation to be the method of choice; Fitz *et al.* (1942) reported a case apparently most satisfactorily treated by this "spray" type of radiation therapy. Acting upon the assumption that polycythemia may be due to an excess of the hematopoietic factor which, through its absence, causes a reversed picture in pernicious anemia, Anderson *et al.* (1938) applied roentgen therapy to the pylorus and duodenum in a single patient and reported good results; however, Stenstrom *et al.* (1940) failed to induce a remission with the same treatment in any of their four patients.

Radio-Phosphorus.—This agent is produced by the bombardment of ordinary red phosphorus by very rapidly moving deuterons generated in the cyclotron. When administered to the patient the agent is quickly concentrated in bone marrow, liver, spleen, bones, etc., in which site its breakdown and decay occurs. It is said that nearly 50 per cent of any given dose is normally excreted during the first six days and that after six weeks no significant amount of radiation can be found in any tissue following a single administration of radio-phosphorus. The agent is given either orally or parenterally and in dosage and at intervals varying according to the hematologic and clinical

status and response of the patient. Fitz-Hugh and Hodes (1942) and Erf and Jones (1943) reported small series of cases in which radio-phosphorus caused very satisfactory remissions in the disease. Unfortunately this agent is very expensive and is not commercially available and indeed its employment must still be considered a somewhat experimental matter.

Venesection and Reduced Iron Intake.—Frequent extensive bloodletting affords temporary relief in most patients, but a more rational type of therapy seems to be that of Dameshek and Henstell (1940) who aimed at producing a state of chronic hypochromic anemia so that the blood viscosity, total blood volume, red cell volume and red cell mass would all be reduced. Their method consists in venesections of 500 cc. twice a week until hemoglobin is reduced to 80 or 85 per cent, red cells to 5 or 5.5 millions, and the hematocrit reading to between 42 and 45 per cent, this usually requiring six to eight venesections. Thereafter the patient is kept on a diet low in iron, which requires avoidance of red meat, meat soups, liver, eggs, rye bread and brown cereals (protein may be derived from fowl once a week, fish twice a week, cheese, milk and legumes). Very good results have been reported with this regimen.

Holbrook (1941) of Milwaukee, reporting an instance in his series of 10 cases in which the patient felt decidedly worse for about a month following one of the blood lettings, interestingly raised the point that a marked discrepancy between the red cell count and the blood viscosity might serve as a contraindication to venesection, for this patient had a blood viscosity of only 5.5 with a count of 8,000,000 when a viscosity of 8 would have been normal.

Hookworm Infestation.—Reports have come out of France of the deliberate induction of hookworm disease in patients with polycythemia vera with the idea of maintaining constant blood loss through the activities of the worms in the intestines. It does not seem to me that much is likely to come of this.

HODGKIN'S DISEASE

Hodgkin's disease is an affection of the lymph nodes of unknown etiology and invariably fatal termination. Males are more frequently affected than females, the majority of cases in either sex occurring between the ages of fifteen and thirty-five. In the usual form of the disease the patient notices a gradual, nonpainful, discrete enlargement of glands in the cervical region; in the beginning the enlargement may be unilateral but both sides are almost invariably involved ultimately. In most cases the axillary and then the inguinal glands, and finally both superficial and deep glands all over the body, become involved. Moderate enlargement of the spleen, and often an increase in the size of the liver, takes place. The patient loses weight and becomes cachectic. General pruritus of a very severe and persistent type is a not infrequent early symptom; very rarely cutaneous lesions of a variegated sort are recorded. A peculiar feature of the disease is the frequent alternating febrile and afebrile periods. The enlargement of cervical, mediastinal, retroperitoneal, or mesenteric groups of nodes may cause symptoms which make the picture a very complex one; involvement of the vertebrae and the cord, when this occurs, is usually a very late manifestation. Initial involvement of the retro-

peritoneal nodes without subsequent mediastinal or peripheral manifestations is infrequent. Hodgkin's disease usually terminates in death within two to three years, though many patients have lived a few years longer than this; cachexia and profound anemia (usually of the hypochromic, microcytic type), mechanical obstruction of one sort or another, or intercurrent infection is usually the immediate cause.

I have presented briefly here only the most usual type, of which there are numerous variations—Middleton (1937) very aptly wrote of the clinical "caprices" of this disease. Histologic examination of an excised node (Meyer, 1941, said that nodes from sites other than the groin are most apt to show affection by the primary disease rather than mere lymphadenitis) shows very definite alterations in structure which cannot be described here for obvious reasons; likewise, the blood and marrow picture in the various types of Hodgkin's disease is a topic that is still in a state of too great confusion to warrant its discussion in a book of this sort.

Wise and Poston (1940), following earlier studies of the same group of investigators at Duke University, reported the coexistence of brucella infection and Hodgkin's disease in 14 consecutive cases in which *B. melitensis* was isolated from blood and lymph node cultures, while failing to isolate the organism from a much larger group of patients with lymph node affections other than Hodgkin's. Forbus and Gunter (1941), also at Duke, isolated *B. melitensis* and *B. suis* from a variety of tissues at 5 consecutive autopsies on cases of typical Hodgkin's disease. Gambrell (1941), however, thought it very strange that the organism should not be *B. abortus*, which is the one most frequently found in this country; she was not able to obtain positive evidence of brucella infection in any Hodgkin's cases at Emory University and in 2 autopsies failed to confirm the findings of Forbes and Gunter. Hoster *et al.* (1944) also failed to find evidence of brucella infection in 35 patients at Ohio State University. So this extremely interesting new approach is at present still merely extremely interesting.

Malpighi (1628–1694) gave the first vague account of this disease, which was fully described by Thomas Hodgkin in 1832. Evidence is accumulating (Steiner, 1941) that Gordon's test, if positive, is of considerable supportive aid in the diagnosis of Hodgkin's disease.

THERAPY

General Therapy.—It is felt to be important that the patient carry out a regimen as for tuberculosis, with rest and fresh air, moderate exposure to sunshine, and a good nutritious diet—"other than that," says Craver, "there is not much to be done."

Irradiation.—The application of radium or x-rays to the enlarged nodes causes a great reduction in their size and consequently leads to considerable amelioration of symptoms. The effect is always temporary, however, and the response to subsequent courses of treatment is less satisfactory. Finally a a point is reached at which there is no response at all. It is quite doubtful whether these agents really extend the length of the patient's life, though there is no denying that they make his existence much more comfortable; it is possible to match every case of exceptionally long survival under irradiation with a case given no treatment at all. Meyer (1941), while by no means decrying the use of the x-ray, nevertheless warned that atelectasis and bronchial reaction and hypersecretion may follow irradiation of the mediastinal

masses. Radio-phosphorus has been useful in some cases, but the employment of this agent is still in the experimental stage (see Erythremia).

Arsenic.—This is the only drug of any "specific" value, the dosage scheme of Forkner (see Leukemia) sufficing here also. The nodes sometimes recede temporarily under this treatment, but, as in the case of irradiation, the ultimate course of the disease is not affected. It does not seem that the response is obtained nearly so often with arsenic as it is with irradiation.

Treatment of Anemia.—It is the consensus that transfusion is often of value in improving the patient's general physical condition; iron is also often helpful. In the rare case, such as that of Townsend and Braunstein (1939), in which the anemia is of the hyperchromic, macrocytic type, liver extract is of course indicated.

Surgery.—It is now generally conceded that the removal of glands by operation is inadvisable in the vast majority of instances. Even the removal of a single gland for purposes of diagnosis should be postponed until it is certain that the procedure is absolutely necessary.

LEUKEMIA

Leukemia is a relatively rare and always fatal disease of unknown etiology, characterized chiefly by the presence in the blood stream of large numbers of abnormal white cells, though in some of the cases there occur at times aleukemic phases in which the white count is found to be below normal. Leukemia is a disease of fowls and the lower mammals as well as of man. It occurs more frequently in males than in females; a familial tendency has not been proved.

Acute myelogenous and lymphogenous leukemia occurs usually in children and nearly always, except for the monocytic form, in individuals under twenty-five years of age. It is rapidly fatal, death occurring usually within a few days to a few weeks at most. The attack is often superimposed upon an acute infection, such as tonsillitis or a furuncle. There is malaise, headache, high fever, bone pain, extreme prostration and a rapidly increasing pallor. Ulcerative lesions appear in the mouth and throat, and marked enlargement of the regional lymph nodes of the neck occurs very rapidly; lymph nodes elsewhere in the body, and also the spleen, are slightly enlarged. Bleeding occurs both externally and internally from the mucous membranes and sometimes also in the fundus of the eye; hemorrhages of the skin are almost the rule and various types of vesicular eruptions are frequently seen. There is very rapid decrease in the number of red cells and the amount of hemoglobin, and marked platelet reduction; at the same time the number of white cells is mounting, though it rarely attains the great height seen in the chronic form of the disease. Immature red cells are also present in large numbers. Lymphocytes and lymphoblasts usually constitute more than 90 per cent of the white cells but sometimes myeloblasts predominate; it is only in recent years that the monocytic form of blood picture is being reported; a few cases of acute eosinophilic leukemia have been described.

Chronic leukemia is insidious in its onset, but usually causes death from anemic exhaustion, hemorrhage, or intercurrent infectious disease, for which the resistance is much lowered, in about three years; a few cases last as long

as ten years and a rare case even longer, but true recovery never occurs. The most prominent symptoms are marked enlargement of the spleen, which causes great discomfort, pallor, dyspnea, dizziness, palpitation, bone sensitiveness, gastro-intestinal disturbances, loss of weight and progressive weakness. Hemorrhage and fever are much later in their appearance than in the acute form of the disease. In lymphogenous leukemia the spleen is not usually much enlarged but there is marked general enlargement of the lymphatic glands, a finding which is quite unusual in the myelogenous type; even the tonsils and the Peyer's patches in the intestine show proliferative changes. The glands are at no time inflammatory. The blood is pale in color, with a low red count and much reduced hemoglobin; immature and abnormal red cells are present. The white count is rarely increased more than to 200,000 and consists almost exclusively of pathologic lymphocytes; the platelets are always reduced. In the myelogenous type of the disease there is an increase in white cells from 100,000 to 1,000,000 or more; polymorphonuclear, eosinophilic and basophilic leukocytes are relatively and absolutely increased, the lymphocytes are relatively reduced but absolutely increased, and immature cells from the bone marrow are present. Blood platelets, usually abnormal in appearance, are initially increased but finally decreased in number. Neutrophilic myelocytes usually predominate, but monocytic and eosinophilic cases are seen; plasma cell cases have been described, and there are other types difficult to classify. Bone marrow changes have been observed to precede the positive leukemic manifestations in the peripheral blood, indicating that bone marrow biopsy might be advisable in all doubtful cases. Chronic myelogenous leukemia occurs most often in individuals between twenty-five and forty-five years of age; chronic lymphogenous leukemia in those between forty-five and sixty. Leukemia is rare in pregnancy; Cross (1944), reviewing the literature and adding 2 cases of his own, brought the total number of congenital cases up to 22. Henshaw and Hawkins (1944) reported that leukemia was recognized approximately 1.7 times more frequently among physicians than among white males in the general population.

In 1935, Schwab and Weiss called attention to the relative frequency of neurologic complications in both acute and chronic leukemias, a fact not much stressed before that time; Merrill and Jackson (1943) stated that renal failure often occurs in leukemia as a result either of obstructive or infiltrative leukemic lesions, stone, or nonleukemic degenerative disease of the kidneys.

THERAPY

Acute Leukemia.—There is nothing to describe.

Chronic Leukemia.—*Irradiation.*—Radium is sometimes applied over the splenic area but roentgen therapy is the more generally accepted method. However, there is certainly still great diversity of opinion with regard to technic, some advocating that attention be directed to the spleen and enlarged nodes only, others irradiating only the chest or trunk, and others practicing "spray" irradiation of the entire body. It seems to be the consensus that irradiation increases the comfort of the patient in most instances and often enables him to remain active longer than without it, but few observers now feel that the length of his survival is much increased. The details of this type of therapy cannot be described here. Radio-phosphorus has been satisfactorily used in a few instances but the matter is still in the experimental stage (see Erythremia).

Arsenic.—In 1931, Forkner and Scott reawakened interest in the use of Fowler's solution by their report of good results. Forkner (1940) stated that he begins with 3 or 4 minims (0.2 to 0.3 cc.) thrice daily in a beverage after meals and gradually increases about a minim a day until 8, 10, or even 15 minims are being taken three times daily. The leukocyte count is said to begin dropping on about the twelfth day with symptomatic remission following shortly. The dose is decreased a minim a day when the leukocyte count is about normal, and when return to 4 or 5 minims three times daily has been accomplished the patient is held at this level. Forkner said that a remission of many months can often be maintained in this way but warned that the drug must be reduced *slowly* as above stated to accomplish this. Arsenic is much used but not all observers feel that it is often of value; for example, Wintrobe and Hasenbush (1939) found it of no value in a small group of lymphogenous cases and of less value than irradiation in myelogenous cases. In their experience the toxic symptoms following arsenic were greater than those following x-ray. Kandel and LeRoy (1937) found it difficult to judge whether the likelihood of inducing hyperkeratosis, neuritis, herpes zoster, and possibly cirrhosis with arsenic outweighed its beneficial effect in the disease. The arsphenamines intravenously are definitely dangerous in leukemia; a number of acute deaths have been reported.

Other Agents and Measures.—On the basis of the alleged causative role of amidopyrine (pyramidon) in agranulocytosis, Terry and Sanders (1934) treated a case of chronic leukemia intensively with phenobarbital (luminal) and amidopyrine; Speidel (1937) also treated a case with amidopyrine alone. Both reported good results, but I doubt the logic of this treatment. Lucia (1935) reported good palliative results in a few cases in which he injected intravenously a freshly prepared 1 per cent solution of potassium antimonyl tartrate, in doses of 2, 3 and 5 cc. on alternate days in series of four to eleven injections. Amidon (1943) obtained some improvement in three of his four cases through the administration of sulfonamides.

Transfusion has often been effectively employed to offset the tendency toward hemorrhage and to relieve the anemia temporarily until it has been possible to irradiate the patient sufficiently to produce results. Kirschbaum and Preuss (1943), reviewing 123 fatal cases of leukemia at the Cook County Hospital, said that repeated transfusions of blood had been the most beneficial treatment, but had given only temporary relief. Morrison and Samwick (1940) tried the intramedullary (sternal) transfusion of normal human bone marrow, but I have heard nothing further of this. Davis and Fitz-Hugh (1939) found that liver therapy has no effect on the anemia of leukemia. Splenectomy is nearly always fatal.

For many years it has been known that intercurrent infections during the course of leukemia are accompanied by a fall in the number of leukocytes. Some years ago Gamble treated 2 cases by the therapeutic production of malaria. In each case there was a prompt fall in leukocytes to half the previous number. Following the termination of the paroxysms, however, the leukocytes rose, in three and six days respectively, to approximately their previous level. Lucherini had better results in his case; the leukocytes fell from 250,000 to 4400 after twelve paroxysms, and at the end of the reported observation of the case, six weeks after paroxysms were stopped with quinine, the blood count was: leukocytes, 5800, erythrocytes, 4,400,000, hemoglobin, 52 per cent; the differential count was said to be normal.

AGRANULOCYTOSIS

(*Agranulocytic Angina, Malignant Neutropenia, Primary Granulocytopenia*)

It does not seem that anyone has fully classified the varieties of agranulocytosis, but the following seem to have attained at least tentative rank as distinctive entities: (*a*) the low-grade chronic type first described by Roberts and Kracke in 1931, and referred to again by Kracke as recently as 1938; (*b*) the type, either acute or chronic in its course, which seems to be associated with excessive splenic lysis of granulocytes and is apparently corrected by splenectomy—first reported by Wiseman and Doan, in 1939; (*c*) the unusual "cyclic" cases in which granulocytopenic episodes, with spontaneous recovery, are alleged to occur at somewhat regular intervals; and (*d*) the type characterized by acute onset, brief fulminating course, and death in the majority of instances. It is the last of these types only which has been studied sufficiently so that its existence as an entity may be granted without reservation, and it is this type alone with which this present article concerns itself. Incidentally, however, one should mention the interesting infectious agranulocytosis of cats, with which a group at the University of Rochester (see Syverton, 1943, in the Bibliography) have been working, though it is not known to bear any relationship to the human disease.

Classical human agranulocytosis was first described by Schultz, in 1922, before which time it had doubtfully existed; mounting then rapidly in incidence to reach a rather alarming peak just before the discovery of its causative agent in 1933, it has since so quickly declined that those who rather rapidly became authorities on the subject now rarely have opportunity to see a case. The rise was all the more "alarming" in that many of the victims were physicians and their families, nurses, technicians and others directly connected with the profession; it is predominantly a disease of adults of the middle and upper (and therefore in America almost exclusively white) classes. The onset and course are often of dramatic suddenness and dispatch: collapse, chill, fever, red throat or ulcerative stomatitis, and possibly ulcerative (without the usual inflammatory reactions) and gangrenous lesions elsewhere throughout the body; sometimes jaundice; very occasionally a slightly enlarged spleen; marked leukopenia and granulocytopenia without notable anemia; stupor and death. Meningitic symptoms have been described in one case (Goadby *et al.*, 1935). Sepsis develops in many patients before the end, the organisms being the normal inhabitants of the oral cavity or lower intestine; but it would seem that complete absence of granular cells for seven days, more or less, is in itself incompatible with life, for some patients die before ulceration, necrosis and sepsis have developed. Though monocytes may sometimes be present in the peripheral blood in abnormally high percentages (Reznikoff, 1938, felt that persistent monocytosis is evidence of good prognosis), the majority of the white cells are usually adult lymphocytes. Marked thrombopenia and a consequent bleeding tendency are probably rarely seen in cases which are unequivocally primary granulocytopenia. The findings of Fitz-Hugh and Krumbhaar (1932), corroborated by those of Custer (1935) and Darling *et al.* (1936), established the primary fault as a maturation arrest of the myeloid (white cell) series in the bone marrow analogous to the erythroblast arrest in pernicious anemia.

The classical experience and experiments of Madison and Squier, reported in 1933, substantiate the statement made above that the causative agent

has been found. In their series of 14 consecutive cases there was a history in each instance of amidopyrine (pyramidon) having been taken immediately prior to the clinical discovery of granulocytopenia: in 7 cases combined with a barbiturate and in 7 cases alone or in combination with drugs other than barbiturates. Five of these patients were being treated in the hospital for other conditions, in the handling of which amidopyrine was being employed, when the agranulocytosis appeared. In the 9 instances in which the drug was withheld there were only 2 deaths (the mortality was 100 per cent in the remainder of the group), both patients having been moribund when the diagnosis was made. One patient, who had had his initial attack eighteen months previously and who had been in a state of complete remission for ten months, took 5 grains (0.3 Gm.) amidopyrine in the evening—within three hours he had a chill, in the morning symptoms had returned and he was found to be almost agranulocytic. Another patient whose first attack had developed during the administration of a compound containing amytal and amidopyrine had recovered from the attack and had had a normal granulocyte count for three weeks when she was given two capsules of the compound; before administration the count was 6850, two hours later it was 3200 and twelve hours later it was 1200. The count then gradually returned to normal. Two weeks later she was given amytal without the amidopyrine and showed no alteration in the granulocyte count. Madison and Squier have now brought their series up to 20 cases, in 19 of which onset of the attack had been immediately preceded by the use of amidopyrine. At the time of their last report, 5 recovered patients who had been under observation for periods of from twelve to thirty-one months, and who had been instructed to avoid the use of amidopyrine, had had no recurrences; one recovered patient had had three recurrences, each following the use of amidopyrine. These studies convincingly showed—as the prior or simultaneous and independent reports of Rawls and Costen, in the United States, and of Videbech, in Denmark, and de Vries, in Holland, had strongly suggested—the causative role of amidopyrine in the malady; Kracke had written several years earlier that drugs of the series to which amidopyrine belongs might be of etiologic importance. Since the publication of Madison and Squier's findings, corroborative reports have come tumbling into the literature throughout Europe, England and America. Plum and Thomsen (1940) showed that in Denmark the decline in case incidence corresponds very closely with decreased consumption of amidopyrine as the result of restrictions upon the sale of the drug: in 1934, 30 cases; in 1935, 14; in 1936, 9; in 1937, 4; in 1938, 1; in 1939, 3. In one Danish hospital, Holten (1934) found that of the 352 patients given amidopyrine during the year before the new discoveries, 239 were women, which is uniquely suggestive substantiation of the drug's etiologic role, since all observers have agreed that the incidence of the disease is much higher among women than among men.

But the belief that amidopyrine is the offending agent is still not universally held; the opponents cite the following facts: (*a*) millions of doses of the drug are taken annually, both by occasional and habitual users, yet but an occasional case of granulocytopenia occurs; (*b*) there are patients who, after the closest investigation, cannot be shown ever to have taken the drug; in some of these instances Reznikoff (1939) believed that excessive fatigue, menstruation and possibly infection may act alone in the causative role; (*c*) instances are on record in which recovery has taken place despite the use of the drug

throughout the attack. It is certainly true that these objections are strong ones, but the following points greatly lessen their appeal. (*a*) As long ago as 1930, Pepper suggested that the disease might be an allergic manifestation. In support of this hypothesis, Squier and Madison (and later several other investigators) have been able to produce granulocytopenia at will on readministration of amidopyrine to individuals whose attack of the disease had followed use of the drug; furthermore, on patch testing with amidopyrine they have sometimes obtained positive skin reactions, granulocyte depression and clinical symptoms. Buus-Hansen and Holten (1935) were unable to confirm this latter finding completely, but Dameshek and Colmes (1936) apparently obtained the skin reaction regularly when they made intradermal tests with a mixture of amidopyrine solution that had "aged" with human serum for several days. If primary granulocytopenia is indeed an allergic phenomenon, then of course it would be no more rational to expect everyone who ingests the drug to develop the disease than to expect all who inhale ragweed pollen to have fall hay fever. Holten (1937), borrowing Quick's hypothesis regarding cinchophen hepatitis, felt that profitable experimentation might be begun upon the assumption that the granulocytopenia is an Arthus phenomenon localized to the leukopoietic part of the bone marrow. (*b*) That no contact with the drug can be demonstrated in some instances is not an insuperable objective. In the first place, it is as a matter of fact very difficult to prove that an individual has not taken the drug in some form. In the second place, no one contends that this drug alone is capable of producing the syndrome; the organic arsenicals, certain of the gold salts, dinitrophenol, acetphenetidin (phenacetin), neostibosan, the sulfonamides, thiouracil and possibly several other drugs have been known to do so occasionally. And if the ailment is allergic in nature the patient may be responsive to some allergen other than one of these drugs—who knows? But the important point is that some individuals do respond allergically to amidopyrine with an attack of primary granulocytopenia. And third, granting that the patient may recover during the administration of the drug (beware of faulty diagnoses!), what of it, in view of the remarks just set down above and of the present limitations of our understanding of allergy?

THERAPY

It is probable that no one has had sufficient experience in the treatment of agranulocytosis to warrant our considering his findings of statistical value; what follows in this place is therefore merely a report of methods that have been used. Kracke (1938) made the point, and Reznikoff (1939) and doubtless many others concurred, that since agranulocytosis is an emergency illness and these remedial measures are not harmful their use is justified even though we lack convincing evidence of their worth. However, it seems to me important to note Madison's feeling that if diagnosis is made before granulocytes have been absent from the peripheral circulation more than twenty-four hours, treatment may be undertaken with good hope of success provided there do not happen to be virulent organisms in the nasal, pharyngeal, or other mucous membranes. Indeed, he thinks spontaneous recovery quite likely to take place under these circumstances; in the 1 case of this sort in which he refrained from employing any therapeutic measures the patient got well. In 2 patients who had high monocyte counts, which he looks upon as a good prognostic sign, Reznikoff also employed no therapeutic agents and recovery occurred.

General supportive measures are of course indicated, particularly cardiac stimulation and the supplying of adequate nourishment in easily assimilable form. Griffith (1932) recorded a case in which he felt that the forcing of fluids through a Jutte tube passed through the nose into the stomach and left in place for seven days, by means of which 120 to 130 ounces (3600 to 3900 cc.) of a high carbohydrate liquid diet (not specified, but I should think that 10 to 15 per cent glucose solution would be satisfactory) were given, resulted in overcoming the dehydration, and causing good kidney function, without disturbing the hematopoietic system or overloading the heart by fluids introduced intravenously. Isolation, in the attempt to prevent infection, would certainly seem to be a rational procedure.

Discontinuance of the Use of Amidopyrine and Related Drugs.—This drug is in use not only under its own name but in many disguised forms as well. The following is the most complete list that I have been able to obtain of the American proprietary preparations that did or do contain amidopyrine, or a compound of it, or that are capable of yielding it in the body in such form as would carry the potentiality of causing agranulocytosis. The list was brought up to date by Kracke, in 1938; from it I have deleted two preparations, "antabs" and "analgia," which the manufacturers claim do not contain amidopyrine, and "allonal," in which acetphenetidin is said to have replaced amidopyrine in January, 1939; to it I have added "causalin" which is said to contain amidopyrine and has been reported in association with attacks of agranulocytosis by Jackson (1938), Dardinski and Lyddana (1939), and McGovern (1940). The list does not include many of the large group of "patent" or secret formula medicines.

Alphebin	Benzedo compound	Midol
Amarbital	Causalin	Mylin
Amidol	Cibalgine	Neonal compound
Amido-neonal	Cinchopyrine	Neurodyne
Amidomine	Compral	Nod
Amidophen	Cronal	Novaldin (novalgin)
Amidos	Dymen	Optalidon
Amidotal compound	Dysco	Peralga
Amifeine	Eumed	Phenamidal
Aminol	Gardan	Phen-amidol
Am-phen-al	Gynalgos	Phenopyrine
Ampydin	Hexin	Pyramidon
Amytal compound	Ipral-amidopyrine	Pyraminal
Baramid	Kalms	Seeqit
Barb-amid	Lumodrin	Yeast-vite

Pentnucleotide.—The hypothesis of leukocyte disintegration products as stimulants of leukocyte production is enticing but it is not certain that very much of practical value has accrued from it. Pentnucleotide therapy has been used with varying success by many physicians all over the world. Its chief champions are still those who introduced it—Jackson and associates—who now recommend that 40 cc. be given each day intramuscularly. Unfortunately there are sometimes fairly severe systemic reactions, which may perhaps be avoided by beginning with lower dosage. Madison believes that it may be wise to continue administration at two- to four-week intervals for some time following recovery.

Adenine Sulfate.—Reznikoff (1933) reported the use of this drug with favorable results in cases that were not severely complicated. The suggested

dosage was 15 grains (1 Gm.) of adenine sulfate boiled in 35 to 40 cc. of physiologic saline solution, given warm, intravenously three times a day for at least three days. Ruskin (1943) extolled the virtues of an iron salt of adenylic acid (ironyl), the contents of one or more ampules of which are injected several times daily in fulminating cases, but precisely what part the use of this agent had played in the recovery of his cases was not easily discernible because of the complicating factor of the employment of many other agents concomitantly.

Penicillin.—Sprague and Ferguson (1944) and Meredith *et al.* (1944) each reported the employment of penicillin in a single case of agranulocytosis which followed the administration of sulfathiazole; in both instances several of the measures which I have been describing here were also employed, but the authors felt that the use of penicillin considerably contributed toward the recovery of their patients. In the 2 cases of Smith and Nichols (1944), in which the attack followed the administration of mapharsen, penicillin was used alone and both patients recovered; it was felt that in these 2 cases control of the secondary infection by penicillin therapy had allowed spontaneous leukocytic regeneration to occur.

Sulfonamides.—Nixon *et al.* (1943) reported three cases of severe agranulocytosis following the administration of sulfadiazine which they felt were cured by the subsequent administration of large amounts of the same drug; it would seem rational to attempt an explanation of this occurrence on the basis of spontaneous recovery from the temporary bone marrow depression. Certainly this experience must be confirmed and extended before one can make general endorsement of the recommendation of Nixon *et al.* that patients who develop agranulocytosis, regardless of etiology, should be treated with sulfadiazine.

Blood Transfusion.—Since no technically satisfactory method of transfusing leukocytes alone is at present available, whole blood transfusions are resorted to, but it must be admitted that the rationale of the method is open to legitimate doubt since the transfusion of 500 cc. of blood can theoretically only raise the leukocyte content of the recipient's body by 6 per cent. However, Doan feels that transfusion is a rational procedure on the basis of its nucleic acid content. Madison feels that it is definitely indicated, especially if there is severe infection of the membranes, and particularly if there is a bacteremia. Witts (1936), in England, believed it not to be indicated, and Jackson (1935) wrote: "Personally I am decidedly against transfusions in this disease"; but Reznikoff (1939) felt that transfusions are not likely to harm the patient. Those who employ them usually give 250 to 500 cc. daily or on alternate days until the leukocyte rise is well advanced. Harkins (1931) thought that the blood of a recovered patient was of especial value in the 1 case in which he used it; Kracke also prefers such blood when it is available.

Leukocytic Cream.—Strumia (1934) gave daily intramuscular injections of leukocytic cream made from the blood of a donor by a special method of his devising. Fitz-Hugh (1935) said the injections are harmless and may be helpful, though they were not of benefit in his personal experience.

Liver.—Liver has been used as in macrocytic anemias. I think it significant that when von Bonsdorff reported 2 liver-treated cases in 1934 he was enthusiastic, but the mood was not sustained when his series had increased to 15 cases in 1936. Of the 4 liver-treated patients in Jackson and Parker's series they remark succinctly "all died." Herndon (1935) reported granulocytopenia

as a terminal event in a patient undergoing vigorous liver therapy for pernicious anemia; on the other hand, Das Gupta and Witts (1937) reported recovery of a "chronic" case treated with liver extract.

Yellow Bone Marrow.—Some years ago there began to be talk of the use of this agent at the Mayo Clinic, and in 1938, Watkins and Giffin read, but so far as I know did not publish, a paper in which it was said that 200 to 400 grains (1 patient took as high as 800 grains) daily of the marrow was employed in 24 patients during 29 attacks; the number of attacks in which they felt adequate dosage was administered was only 21, recovery occurring in 19 instances. The concentrated preparation (Armour), prepared and used by Marberg and Wiles (1938) in a small series of cases, was given in a dose of 1 to 5 cc. three times daily by mouth.

Pyridoxine (Vitamin B_6).—Cantor and Scott (1944) gave pyridoxine hydrochloride intravenously in doses of 125 mg. to 200 mg. daily in 3 cases of agranulocytosis resulting from the toxic action of three chemically unrelated drugs; in one of the cases pyridoxine was used alone, in another one blood transfusion was also given, and in the third repeated blood transfusions and pentose nucleotide in large dosage were employed in addition to the pyridoxine. In each of the 3 cases, however, the symptoms cleared up rapidly after the pyridoxine therapy was instituted and it was felt that probably this agent acted by direct stimulation of the myelocytic elements of the bone marrow.

Nonspecific Proteins.—Attempts to stimulate leukocytosis through such measures as the intramuscular injection of turpentine, milk, or bacterial products are illogical since in the presence of maturation arrest in the marrow there are no leukocytes to be mobilized. One of Jackson's cases developed in the midst of an attack of boils.

Roentgen Therapy.—X-ray in this disease is certainly a two-edged sword, as pointed out by a number of observers, and there is no escaping the fact that the difference between the dose which will stimulate the hematopoietic tissues and that which will destroy them cannot be accurately known to roentgenologists since it most probably varies widely from individual to individual; therefore the assumption upon which therapy is based, namely, that there is a fixed stimulatory threshold below which primary destruction of cells does not precede regeneration, is—well, assumption. Doan, indeed, believes that such good results as may be obtained are directly chargeable to destruction of myeloid foci with a liberation of autogenous nucleotide and resultant initiation of maturation; Madison concurs in this view, but the only 2 x-ray treated cases which he has seen terminated fatally.

Local Therapy.—The usual treatment for severe stomatitis is considered to be indicated by most observers (see methods under Stomatitis), but some think that the continuous swabbing of the lesions with various antiseptic solutions serves only to disturb the patient needlessly. Madison believes that the local application of antivirus is probably of considerable value. Griffith made daily applications of an erythematous dose of ultraviolet light to lesions in which streptococci predominated, hoping for the same good result sometimes obtained in erysipelas. As a matter of nursing detail the utmost attempts to maintain asepsis and to prevent cross contamination are mandatory.

THE PURPURAS

Nowhere in medicine today is there greater confusion than in this subject of the purpuras, the reason being of course our lack of knowledge. I am sure the present article will not satisfy specialists in this field; it certainly does not satisfy me, but it represents the best I have been able to do within the limitations of space and time and my own inadequate grasp of the subject.

Thrombocytopenic Purpura (Purpura Haemorrhagica).—This entity, which is probably the one with which Werlhof was dealing in 1735, is preeminently a disease of the young, though no age is exempt; females are more often affected than males. There is marked diminution in the number of circulating blood platelets, which may be brought out by repeated counts if a single one does not demonstrate it; prolonged bleeding time and little or no clot retractility; normal or nearly normal coagulation time; evidences of normal blood regeneration; and a positive constrictor or armband test (Rumpel-Leede). The spleen is usually not palpable. Spontaneous capillary hemorrhages may occur into any of the tissues, bleeding from the uterus, nose and mouth, and into the retina being the most common. Hemorrhage into basal ganglia may cause fever, mental disturbances, convulsions, etc. The bleeding often begins without warning and persists intermittently for days or weeks, death resulting in severe cases from exsanguination. A chronic form of the disease is recognized, which does not develop from the acute form but is chronic throughout. These patients give a history of having bruised and bled easily for many years before the onset of the attack in which diagnosis is made from the blood findings. Such individuals bleed intermittently during a number of years, some dying and others apparently recovering completely. Cases have been reported in which a rapid fall in platelets and the appearance of purpura were associated with menstruation, with remissions between and recurrence with the succeeding periods; indeed it would seem from the work of Pohle (1939) that in many normal women there is a cyclical variation in the number of platelets in regular relation to the menstrual cycle. Goldburgh and Gouley (1940), and Snaith (1940), described cases in which menorrhagia was the only or the first symptom of thrombopenic purpura. Congenital purpura seems to be an established fact: Davidson (1937) reported a purpuric infant born to a mother whose platelet count had always been low during the several years after the removal of her spleen because of purpura; Whitney and Barritt (1942) reported the case of a woman who, becoming twice pregnant after splenectomy for thrombocytopenic purpura, in each instance was delivered of an infant that succumbed to thrombocytopenic purpura in the neonatal period. There seems to be also a very rare type of thrombopenic purpura (Altschule, 1942) characterized by the formation of numerous platelet thrombi in the capillaries throughout the body, rapid progression, failure to respond to transfusion and splenectomy, and the uniform occurrence of icterus and cerebral manifestations.

The clinical manifestations in thrombopenic purpura are currently believed to be due to an idiopathic reduction in the number of platelets, but perhaps the fault may lie not so much in a quantitative as in a qualitative alteration in these elements. Conversely, abnormal permeability of the capillaries is held jointly responsible in some cases by some observers (Madison and Squier, 1940); the findings of Leonard and Falconer (1941), studying the experimental condition in the guinea pig, somewhat supported this position. A hypothetic toxin, acting upon either the platelets or the capillary walls, has been postu-

lated. Some students of the disease contend that the spleen removes excessive numbers of platelets from the circulation; Troland and Lee (1938) reported that a substance extracted from the spleens of patients with thrombocytopenic purpura and injected into rabbits caused a reduction of circulating platelets in these animals—after several independent workers had failed to confirm the findings, Rose and Boyer (1941), and Cronkite (1944), seem both to have confirmed and extended them. Limarzi and Schleicher (1940) championed the view that the disease is due to the production by the spleen of a factor which causes faulty maturation of the megakaryocytes in the bone marrow; Wiseman *et al.* (1940), however, did not find evidences of such an effect in their marrow studies. Madison and Squier proposed the hypothesis that some cases of thrombopenic purpura rest upon an allergic basis.

Simple Nonthrombocytopenic Purpura.—In these cases the chief fault seems to be chargeable to an idiopathic alteration in the permeability of the small vessels, since often there is no abnormality in the blood at all or merely a prolongation of the bleeding time; occasionally, however, both failure of clot retraction and prolongation of the bleeding time are seen, but by definition marked reduction in the platelet count cannot occur in this group. The purpuric lesions appear in crops which recur at intervals of weeks to years, often without any other symptoms, though many patients complain of joint pains especially in the knees; with advancing age this type of purpura tends to die out altogether. Davis (1939) described an hereditary familial form of this disease.

Secondary Purpuras.—Purpuric manifestations are observed during the course of many disturbances, of which the following is a partial list: infectious diseases, such as hemolytic streptococcus septicemia, meningococcemia, bacterial endocarditis, miliary and generalized tuberculosis, scarlet fever, typhoid fever, etc.; focal infections especially in children; scurvy; vitamin K deficiency; endocrine disorders (the triad of sepsis, purpura and bilateral adrenal hemorrhage, seen almost exclusively in children, is called Waterhouse-Friderichsen syndrome); aplastic anemia; acute leukemia; excessive irradiation; senility; cachectic states, especially if due to malignant disease; chronic liver and kidney disease. It is thought that these purpuras are not of the thrombopenic sort as a rule, save in those instances when direct disturbance of bone marrow function has occurred, but as a matter of fact the group has not been exhaustively studied. The purpuric signs disappear with recovery from the primary disease, deficiency, or intoxication.

Schönlein-Henoch's Disease.—In this type of purpura the attack begins with malaise, fever, sore throat and polyarticular pains, all of which usually precede by some time the eruption which often partakes of the nature of purpura, urticaria and erythema in combination. Or there may be abdominal or renal crises due to the extravasation of blood into the intestines or kidneys. In some instances purpuric lesions fail to appear in the skin, which makes the diagnosis by no means easy. All the manifestations in this disease seem to be ascribable to alterations in capillary permeability, which are believed to rest upon an allergic basis.

THERAPY

Unquestionably the most important single factor in treatment is to make every effort to determine the type of purpura with which one is dealing, since a major surgical procedure which may be necessary and life saving in one

type would be contraindicated and absolutely inexcusable in another. Likewise the failure to recognize an underlying drug intoxication, or an ascorbic acid or vitamin K deficiency or a neoplastic malady or leukemic blood dyscrasia, might have the direst results. The subject is confusing admittedly, but accurate diagnosis is mandatory notwithstanding.

Thrombocytopenic Purpura.—*The Allergic Approach.*—A sufficient number of case reports has now accumulated to warrant the careful study of every patient from the standpoint of drug sensitization; instances in which attacks have been definitely ascribable to the following agents have come to my attention: organic arsenicals, gold salts, benzol, sedormid, nirvanol, phenobarbital, quinine, ergot, dicoumarol, sulfonamides; cases have also been reported in association with the use of hair dyes and leg stocking color preparations. Foods to which the patient responds allergically have also been indicted. Squier and Madison (1937), by limiting treatment to such dietary manipulation as eliminating foods suspected on the basis of history and skin tests, were able to effect striking clinical improvement and gradual marked rise in platelet level in their 3 patients. Dutton (1938) reported similar success in the single case which he treated in this manner, and Farrar and Roxby (1943) demonstrated the allergic nature of one of their cases. Several observers have rather airily dismissed this sort of approach simply by saying that in their experience the allergic constitituon did not seem to be involved in the mechanism of purpura, but I have seen no evidence in their reports that the painstaking and expert sort of allergic study required here had been made in their cases. Splenectomy is a radical procedure, transfusion is only a palliative measure; if there is a chance that meticulous allergic study might solve the puzzle in many of these cases it seems unfortunate that more of them are not submitted to such study.

Splenectomy.—It certainly seems to have become the consensus in the profession that splenectomy is the treatment of choice in severe cases. Kracke (1941), not himself a surgeon, said "I have never seen a severe case of this disease that finally did not require splenectomy. . . . It seems to me that treatment with medical measures is merely temporizing until the inevitable time comes for removal of the spleen." Sometimes the staunching of the hemorrhage occurs before the patient has been removed from the table or even before the abdominal incision has been closed. According to Elliott (1939), of the Spleen Clinic of the Presbyterian Hospital in New York, the results are highly satisfactory in about 85 per cent of cases; Robertson (1938) suggested that some of the failures might be due to the presence of accessory spleens elsewhere in the body; Pernokis (1942) felt certain that one of his patients died as a result of hyperplasia of an accessory spleen noted during the operation but not removed, and Evans and Perry (1943) have noted the persistence of symptoms under such circumstances. Of the several follow-up studies available the one which extended over the longest period seems to be that of Vaughan and Wright (1939), whose 6 patients were free from bleeding phenomena, and 4 were known to show normal platelet levels, at periods of from ten to fifteen and one-half years after operation. Splenectomy has been performed late in the period of gestation, sometimes without disturbing the pregnancy. But not even the warmest advocates of this measure rush their patients at once into the operating room. Witness Giffin, who from the standpoint of a physician and not a surgeon reviewed the Mayo Clinic experience in 1936: in not one of the cases in this series was it felt necessary to operate

within ten days of the onset—days in which other measures, especially transfusion, were being given full trial. In the Johns Hopkins Hospital series, reported by Wintrobe *et al.* in 1937, splenectomy was performed in only 19 of 62 cases.

The reason for the apparently undeniably remarkable effect of splenectomy in many cases is not at hand, for usually the platelet count does not reach normal until many days after hemorrhage has ceased. Sometimes postoperatively the platelet count goes down again to the earlier level and yet the patient remains free of symptoms; Askey and Toland (1933) stated that many patients show clinical improvement after removal of the spleen without the blood reflecting this change in a single particular. However, Nygaard (1940) said that study of any large group of cases shows that the least satisfactory results are found where more or less marked reduction of circulating platelets follows operation. It is also true that patients sometimes have recurrence of symptoms though the platelet count has mounted to and remained above normal postoperatively (Brown and Elliott, 1936). Whether or not operative trauma alone may suffice to explain the good results is a question which cannot be lightly smothered; Giffin (1936) admitted inability to refute the assumption categorically but felt that the limited data available strongly indicated the useful office of removal of the spleen itself. An observation not to be lightly overlooked, however, is that of Steiner and Gunn (1931), namely, that operations in rabbits involving an amount of trauma comparable to that during removal of the spleen induce a platelet rise differing neither in time of occurrence, degree or duration from that following splenectomy; Adams (1944) found a substantial postoperative rise in the level of the blood platelets quite commonly, though not without exception, in 41 patients who had undergone various types of operation.

Transfusion.—The object of transfusion in purpura is not solely to supply blood lost through hemorrhage, since the anemia usually rapidly disappears through the body's own spontaneous efforts once bleeding ceases, but also to introduce platelets in the hope of stopping hemorrhage; bleeding usually begins when the normal platelet count of 250,000 to 400,000 has fallen to 50,000 to 75,000, but not invariably. In an earlier day, Larrabee, among others, arguing that a single transfusion seldom increases the patient's platelet count more than 20,000, advocated large transfusions of as much blood as the donor could safely give; the patients being mostly young persons with normal hearts, he felt there was little danger from overtransfusion. Many observers of that period also believed that citrated blood was inferior to untreated blood. Nowadays, however, both positions are reversed: Jones and Tocantins (1933), and Patek (1936), expressed the consensus in advocating frequent—daily in some instances—transfusions of 100 to 300 cc. of citrated blood. Wiseman *et al.* (1940), however, advocated transfusions of full size (500 cc. for adults) and saw no difference in effectiveness between citrated and untreated blood; Madison (1944) also said that blood should be given in sufficient quantity to replace all that has been lost. Potts' (1932) results with 8 to 10 cc. of whole blood given intramuscularly probably were based upon some mechanism other than the supplying of platelets, for Wiseman *et al.* declared categorically that these injections are of no value. It is interesting to note that the native African disease "onyalai," now considered to be essentially thromocytopenic purpura, which Blackie (1937) and numerous others have treated satisfactorily with small intramuscular injections of blood, has been found,

at least in the experience of Stein and Miller (1943), to respond better to full transfusions of blood.

Splenic Irradiation.—Most men have not as yet become convinced of the worth of this measure. However, Madison, Squier and Morton (1943), of Milwaukee, reported a small series of cases which suggested to them that irradiation might be a valuable temporary measure in stopping spontaneous vascular leakage in selected cases of purpura whether or not there is an associated thrombocytopenia or hypoprothrombinemia. They felt that if such an association exists it is important to eliminate the vascular leakage promptly, and further that failure of response to irradiation strongly suggests that purpura is secondary to progressive malignant disease, while on the other hand satisfactory response may suggest that if other therapy fails splenectomy is likely to be beneficial.

Miscellaneous Agents.—Many remedies have risen and fallen through the years; the following may be currently mentioned: (*a*) Congo red: in 4 cases resisting other treatment Brühl (1933) reported prompt arrest of bleeding by intravenous injection of 10 to 20 cc. of this dye in 1 per cent aqueous solution. Taliaferro and Haag (1937) showed that such dosage causes a decrease in coagulation time in normal individuals, but Richardson (1939) was unable to confirm this finding; the rationale of Congo red employment seems very doubtful. (*b*) Ascorbic acid (cevitamic acid, vitamin C): Junghans (1935), Vogt (1935) and Miller and Rhoads (1936) reported successes with this agent. But Davidson (1937), employing the recommended dosage of 100 to 300 mg. intravenously daily for seven to ten days, did not favorably influence either the platelet level or the symptoms in his 3 patients; Stephens and Hawley (1936), and Wright and Lilienfeld (1936), were also doubtful of the value of this vitamin approach. (*c*) Hypercalcemia: Lowenburg and Ginsburg (1936) incidentally noted cessation of bleeding in a patient in whom hypercalcemia had been induced. Recalling the experience later, they deliberately employed the method in a second patient whose purpuric symptoms did not yield to other measures; subcutaneous injection of 3 cc. (60 units) of parathyroid extract and intramuscular injection of 10 cc. of calcium gluconate solution were made daily for three days, the patient being a child of seven years. Serum calcium and phosphorus rose very high but reverted to normal promptly after cessation of treatment. Toxic manifestations during the hypercalcemia were vomiting, weakness, apathy and lethargy. With the establishment of hypercalcemia definite symptomatic and hematologic improvement set in; subsequent examinations after discharge from hospital revealed the patient to have remained in a practically normal state. Ainsworth *et al.* (1937) succeeded with this treatment in their 2 cases, and Levine and Michelson (1940) in their single case; Farrar and Roxby (1944) also felt its use was valuable during one phase in a very complex case reported by them. Mathewson and Cameron (1937) failed in their case, and both Rosenthal (1939) and Wiseman *et al.* (1940) reported unfavorably, but they gave no details of their cases. (*d*) Snake venom: the Council on Pharmacy and Chemistry reviewed the record of this agent in 1940 and did not find it acceptable. (*e*) Sesame oil: Olson (1939), in 2 cases, failed to confirm the earlier report that this so-called "T-factor" is of value. (*f*) Citrin (vitamin P): the evidence that this agent is of value in thrombocytopenic purpura *per se* is not convincing; indeed its employment provoked a severe attack in one of the patients of Farrar and Roxby (1944).

Simple Nonthrombocytopenic Purpura.—It is obvious that there is no warrant for the use of drastic measures in these cases. That the allergic approach is most promising was indicated in the studies of Eyermann (1935) and Diamond (1936).

Secondary Purpura.—The treatment is that of the underlying major disturbance.

Schönlein-Henoch's Disease.—The fact is well established that these attacks are practically always of an allergic nature; treatment therefore consists principally in the search for the guilty allergen and the attempt to eliminate it from the diet or environment or to desensitize the patient to it. Of course splenectomy and all other drastic measures are contraindicated; cases are on record, however, in which laparotomy has revealed intussusception and true hemorrhagic appendix. Possibly one should note Jersild's (1938) single case in which all the symptoms disappeared under vitamin P (citrin) therapy and returned when this therapy was stopped; beginning administration was 50 mg. daily intravenously, later dosage was 20 mg. twice weekly intramuscularly.

HEMOPHILIA

Hemophilia is an hereditary hemorrhagic disease of unknown etiology, which is transmitted by the female but occurs only in the male. Macklin's (1928) studies showed that (*a*) a man afflicted with hemophilia will have no hemophilic children provided he marries a woman who is not a carrier; (*b*) the sons of such a man will be normal and unable to transmit the defect; (*c*) his daughters will all be carriers, though outwardly normal, liable to give the active disease to half of their sons; (*d*) half the daughters of a woman who is a carrier are apt to be carriers themselves, transmitting the defect, as their mother did, to half their sons as the active disease, and to half their daughters who will be carriers in their turn; half the daughters and half the sons of a woman who is a carrier are apt to be normal; (*e*) since, in a hemophilic family it is impossible to tell which women are carriers until they reproduce, it is advisable for all women in such a family to refrain from having children; (*f*) the only persons in a hemophilic family who can marry with impunity are the unaffected males and their descendants. Macklin's (1939) later study indicates that there is no adequate basis for the idea that the sex ratio is disturbed in hemophilic families in favor of perpetuating the malady. There are obscure types of the disease which in the matter of heredity are not easily fitted into the classical framework, but these pages are of course not the place for an analysis of such rarities.

The characteristic abnormality in the blood of individuals with classical hemophilia is prolongation of the coagulation time, an alteration, however, which varies apparently from day to day and perhaps even from hour to hour; therefore at some periods the patients are much more likely to bleed than at others. Bleeding time, clot retraction (once clotting begins), and the platelet count are normal; the Rumpel-Leede test for capillary erythropermeability is negative. Quick *et al.* (1935) found prothrombin quantitatively normal but thromboplastin deficient, while Brinkhous and his associates

(1939) reported an abnormally slow conversion of prothrombin into thrombin, such as would result if thromboplastin were sluggishly liberated from the platelets. Tocantins (1942) found the antithromboplastic activity of hemophilic plasma several times that of normal type, which he felt explained both the slow transformation of prothrombin into thrombin and the low thromboplastin content of citrated hemophilic plasma. It seems almost certain that neither calcium nor fibrinogen disturbances are present. In the years since 1936, Patek, Pohle and their associates in this country, and Bendien and Van Creveld in Holland, have been presenting evidence in support of the view that blood plasma contains a specific "globulin-substance" which accelerates clotting and is deficient in hemophilic blood. Howell (1939) seemed to feel that this substance is practically identical with plasma thromboplastin, but Quick (1942), in his monograph on the hemorrhagic diseases, rejects the evidence regarding this "globulin-substance," reiterates that prothrombin, fibrinogen and calcium are normal and thromboplastin deficient in hemophilic blood, says that there is much indirect evidence of abnormal stability of the platelet, and expresses himself certain that the final solution of the hemophilic problem will be contingent upon finding the factor responsible for the stability of the platelet. Perhaps the hypothesis of Pennell (1943) is of interest in connection with this latter viewpoint, namely, that a conjugation phenomenon which permits the platelets to use the surfaces of red cells for their mass disintegration is markedly reduced in hemophilia.

The disease usually makes itself apparent at an early age. External hemorrhage of an oozing type occurs following the most trivial injuries; spontaneous bleeding in the viscera is rare, except in the kidneys, and bleeding into the central nervous system is very unusual. Obstinate epistaxis is common, so also are hemorrhages into the muscles and skin and about the joints; the latter ultimately cause deformities much resembling those of tuberculosis or low-grade arthritic conditions, but in the acute stage differentiation must be made from traumatic synovitis, acute rheumatic fever, acute pyogenic arthritis, gonorrheal arthritis and osteomyelitis. Hemophiliacs nearly always succumb before adulthood is reached, either during the course of a profuse hemorrhage or from the cachexia and anemia resulting from frequently repeated sublethal bleedings.

In the Babylonian Talmud (second century, A.D.) it is stated that circumcision is to be discontinued in a family in which it has caused two successive fatalities; this is looked upon as the earliest reference to hemophilia. The first clear account in modern literature was that of Otto, in 1803; the disease was named by Schönlein in the middle of the nineteenth century. Hemophilia is of exceedingly rare occurrence in Negroes.

THERAPY

Blood transfusion usually hastens coagulation for a period which is long enough for clotting to take place; the duration of the effect of a transfusion is highly variable but is usually a matter only of hours and not of days, so that unless one of the nonbleeding phases characteristic of the disease happens to begin shortly after a transfusion is given it is apparent that transfusion is of very limited value as a measure to keep the patient alive indefinitely. It seems that 100 cc. is as effective as 500 cc. Patek (1940) felt that unless the patient urgently needs hemoglobin a transfusion of 100 cc. at twelve-hour intervals is preferable to 600 cc. at three-day intervals; he also found

pooled citrated plasma just as effective as whole blood. Johnson (1942) successfully used plasma which had been prepared for storage by the now familiar lyophile method. Munro and Jones (1943) reported one case studied over a period of four years in which it seemed to them that repeated transfusions of either whole blood or plasma lost their effectiveness and even possibly had a detrimental effect. In 1932, Lawson *et al.* not only did not transfuse their patient, but since severe hemorrhage results in decreased clotting time, they actually deliberately bled him. Five hundred to 600 cc. were withdrawn every five to six weeks, apparently with good symptomatic results; indeed, in a subsequent report, it was stated that this patient had been bled about once every six weeks with good results until the time of his death in another hospital in 1939; the successful employment of venesection in hemophilic crises in two other members of this patient's family was also reported. Hemophiliacs appear to have an accelerated rate of blood production, which insures rapid recovery from hemorrhage of ordinary extent; iron therapy is sometimes helpful, but liver-stomach preparations are not needed. These individuals, especially those who are only mildly afflicted, can be carried safely through surgical procedures if transfused just before incision and repeatedly during the healing stage of the wound.

The literature with regard to the ordinarily available preparations of tissue thromboplastin, which are injected intramuscularly, is highly contradictory and it is my impression that the men who have had most experience in hemophilia do not consider them of any value. But with regard to the globulin-substance of Patek and Pohle it is perhaps too early for anyone to have formulated a definite opinion since the substance is difficult to prepare and is not yet generally available. Lozner and Taylor (1939), of this same group of investigators, prepared a euglobulin-substance which was thought to have some advantages over the first preparation—so the investigation is seen to be continuing and one may hope that something of a generally applicable nature will result. Eley *et al.* (1936) prepared an anticoagulant substance (presumably a tissue thromboplastin) from human placenta, which has the advantage of being suitable for administration by mouth; but this too is still in the experimental stage. The substance which Timperley *et al.* (1936) obtained from egg white has apparently come to little; at least I have seen no recent reference to its employment. Protein sensitization has been tried off and on for years but there is no convincing evidence of its value. The estrogenic substances, toward which we looked for a time so hopefully, are now recognized also as failures. Recently there has been a flurry of interest in oxalic acid and the proprietary preparation, koagamin, which resulted from these studies; but Johnson (1941), at the University of Rochester, used both oxalic acid and the proprietary preparation without effect in 5 cases of hemophilia. Tagnon (1944) obtained a significant shortening of the coagulation time following the intravenous injection of trypsin in 2 patients, but he felt uninclined to recommend the employment of this agent unless further investigations are able to reduce its toxicity.

In the control of accessible hemorrhage none of the older hemostatics has shown any consistent worth; perhaps the one with the most honorable record is tannic acid, used as a dusting powder. There are favorable reports on the use of snake venom in small series of cases. In England, Macfarlane and Barnett (1934), and Baker and Gibson (1936), employed Russell viper venom in a dilution of 1:10,000; in the United States, Rosenfeld and Lenke (1935)

used 1:5000 tiger-snake venom. McGavack (1940) did not succeed with venom solutions but used viper venom in powder form successfully in one case of bleeding following tooth extraction; he also successfully employed the powdered globulin-substance of Pohle and Taylor, previously mentioned. Sole (1935) reported good results from applying iodoform tampons saturated with human milk, and Castex and Pavlovsky (1942) controlled a dental hemorrhage with a modified form of this treatment; anything is worth trying perhaps. Where stitching is necessary, catgut sutures which will not have to be removed later, elevation of the part if possible, and absolute rest, are about the only things to resort to. According to Birch (1933) hemorrhages from the loosening or loss of deciduous teeth are best treated by making a mold of soft wood, cork, or gutta-percha which fits over the gum and fastens tightly to the teeth on either side of the bleeding point; she lines the mold with a thin layer of cotton soaked in ovarian extract (others use powdered snake venom), and keeps the patient on a liquid diet. Extraction of a tooth should take place only if absolutely unavoidable; before the tooth is removed a mold such as the above should have been prepared to hold cotton in place in the cavity. In 2 instances of bleeding tooth sockets, Warner *et al.* (1939) promptly controlled hemorrhage by spraying on their purified thrombin preparation.

Of course hemorrhage into a large joint calls for rest of the joint, with mechanical immobilization if necessary, until pain disappears and the blood is largely absorbed; salicylates are helpful. When there is intense pain the question arises as to the possibility of aspiration. Key (1932) said that it has been carried out a number of times without ill effects, but probably in all of these instances the patient was, as in his own case, in a nonbleeding phase. Certainly fatal hemorrhage and infection have resulted from such aspirations. Orthopedists are rather impatiently awaiting the discovery of a medical cure for hemophilia so that they may begin the correction of the deformities, but I doubt that many of them are daring to undertake open operations at the present time.

HEMORRHAGIC DISEASE OF THE NEWBORN

(See *Vitamin K Deficiency*)

HYPOPROTHROMBINEMIA

(See *Vitamin K Deficiency*)

HEMORRHAGE IN OBSTRUCTIVE JAUNDICE

(See *Vitamin K Deficiency*)

CIRCULATORY DISTURBANCES

FUNCTIONAL DISTURBANCES OF THE HEART

Occasionally a functional heart disturbance in an individual of fairly robust mental and physical status will follow upon the shock of a sudden cardiac death in a near associate, but cardiac neuroses are usually seen in persons of definitely neurotic type and often with a history suggestive of neurotic ancestry. There is complaint of transitory palpitation, rushing of blood in various parts of the body, throbbing and many other symptoms which are described with the particularity so habitual to the neurotic. When there is pain it is usually felt over the left chest where the heart is supposed to be rather than under the sternum. In the condition known as neurocirculatory asthenia (effort syndrome, soldier's heart, irritable heart), the symptoms—giddiness, faintness, palpitation, precordial pain and breathlessness—are the symptoms of effort and mark the patient as one who is physically inadequate to the ordinary stresses and strains of an active life. In War I effort syndrome was a serious problem especially in the British Army, but Jones and Scarisbrick (1942) stated early in War II that the number of cases being encountered was proportionately much smaller; in our own country, too, every effort has been made to screen out these individuals at the induction centers, but in spite of this effort Brown (1944) was obliged to report that in a twelve-month period at a large Army hospital there were nearly ten times as many soldiers with this syndrome as with organic heart disease. As a result of studies upon Navy personnel, Master (1944) stated his belief that effort syndrome is really the result of a congenital or constitutionally small heart and should therefore no longer be considered merely a nervous or functional disorder. Friedman (1944) observed an episodic type of fever in about 36 per cent of 30 young soldiers, a finding which he thought evidenced thermal imbalance as the result of abnormal activity of the hypothalamus; in 65 per cent of Steven's (1945) 40 patients there was a flat sugar tolerance curve.

THERAPY

Patients with undoubted cardiac neuroses comprise a very considerable portion of the "heart" cases seen in an average general practice, and the fact that the elements of their treatment can be set down in a relatively few lines of print by no means justifies a contemptuous attitude toward the group. The more robust will be cured by complete examination and the reassuring statements of a doctor in whom they have confidence, but what is needed by the majority of the patients is just exactly the hardest thing in the world to supply, namely, an entire readjustment to life. If there is some one thing which is causing the basic unhappiness upon which the neurosis is engrafted, the bringing of that thing out into the open and the attempt to reconstruct a life in which that particular fact is accorded no more than its proper share of importance, will oftentimes greatly relieve the patient, though if he is basically neurotic the relief will usually be only temporary. In no case must a cardiac neurotic be permitted to continue in the belief that he has the least

thing the matter with his circulatory apparatus, but there are ways and ways of assuring him of this fact. Perhaps the best method is to demonstrate his freedom from symptoms while enjoying some diversion in which he is for a time freed from his inordinate load of cares; to ridicule or to scold is almost certainly to toss him to the quacks.

The avoidance of physical and mental fatigue is important and can usually be accomplished in some degree if the patient is at all tractable.

In neurocirculatory asthenia (effort syndrome) definite attempt to build up the patient's tolerance for that amount of physical exertion which is necessary in his occupation should be made, but it is seldom possible to bring him up to the normal of physical endurance. Carefully graded exercise, with special stress upon the necessity of obtaining not only a long night's sleep but a midday rest as well, is desirable. White (1942) said that it was found wise in England to treat the average run of the cases of neurocirculatory asthenia that arose in the armed forces during War II as ordinary medical cases of fatigue without referring them to either cardiologist or psychiatrist, in this way avoiding overemphasis of either heart or mental state in the patient's mind. However, I think that most men in our own Army wanted these men out of the way as soon as possible since they interfered in almost every training program, and when they were excused from certain duties they sometimes, according to Brown (1944), started an epidemic of the same symptoms in their outfit.

PERICARDITIS

Acute pericarditis rarely occurs except as a complication of one of the infectious diseases, particularly tonsillitis, sinusitis, tuberculosis, scarlet fever, acute rheumatic fever, pneumonia and sepsis (septicemia), though it occasionally occurs as a postoperative complication and as a terminal condition it is sometimes recognized in chronic nephritis. In fibrinous pericarditis without effusion the symptoms are those of the primary disease plus pain in the precordium, or referred to other parts of the body, and a characteristic friction rub heard upon auscultation. When effusion occurs the patient usually becomes anxious, more or less cyanotic and dyspneic, and often very restless. Pressure on nerves and other structures may cause cough, aphonia, difficulty in swallowing, hiccup, vomiting, and so on. The pulse rate usually rises very high and becomes irregular. The area of dulness at the base of the heart is increased and there may be actual bulging of the precordium; the apex impulse usually disappears. As the fluid increases the friction rub diminishes and, with a large effusion, the heart sounds are no longer audible. Despite the glibness with which it is usually described, pericardial effusion is by no means always easy to diagnose. The prognosis in fibrinous pericarditis is always good; in the effusion cases, if the fluid is tuberculous or becomes purulent (suppurative pericarditis), death is the usual outcome, but in rheumatic cases the fluid is usually absorbed. Acute pericarditis was probably first discovered by Avenzoar, of Cordova, in the twelfth century.

There is also a chronic type of constructive pericarditis known as "Pick's disease." Its chief characteristics seem to be (*a*) insiduous onset of dropsy

in a young person without nephritis or a markedly abnormal heart; (*b*) enlarged liver, ascites and prominence of jugular veins; (*c*) low systolic arterial pressure and a small pulse pressure and paradoxical pulse. History of antecedent pericarditis or polyserositis is a helpful clue. The patients are condemned to semi-invalidism unless properly treated.

THERAPY

The treatment of acute pericarditis is the treatment of the primary disease. An ice-bag placed upon the precordium in the robust, or hot applications in the puny, asthenic individual, are usually successful analgesic measures. Codeine, 1 grain (0.065 Gm.), morphine, $\frac{1}{4}$ grain (0.015 Gm.), or dilaudid, $\frac{1}{32}$ grain (0.002 Gm.) should not be withheld if pain is sapping the patient's strength; perhaps demerol in a dose of $2\frac{1}{2}$ grains (0.15 Gm.) should be preferred for its lack of opiate-like action on the gastro-intestinal tract. Salines, or enemas, are definitely indicated to prevent abdominal distention or straining at stool, both of which increase the load upon the heart. Aspiration of fluid brings such great relief in the effusion cases that it is held to be advisable to employ the procedure early and frequently, except perhaps in the rheumatic cases where remarkably quick subsidence of the effusion sometimes takes place. When the fluid becomes purulent, the attempt to establish surgical drainage must be made at once; Bigger (1939) and others stressed the necessity of making every effort to arrive at an early diagnosis since surgical procedures alone offer whatever chance there may be of cure. Certainly both the sulfonamides and penicillin have been failures when given systemically in acute suppurative pericarditis, but perhaps I should note here the report by Allison and Loughlin (1945) of a case in which penicillin instilled locally into the pericardial sac apparently contributed to the patient's recovery.

In Pick's disease the outlook has been completely changed through the introduction of surgical technics facilitating removal of a portion of the thickened pericardium; relief of symptoms and "cure" often result. In preparing these patients for operation, Stewart (1942) said that he restricts the salt and fluid intakes, uses a high protein diet and diuretics, and does not give digitalis unless there is a superimposed auricular fibrillation.

ENDOCARDITIS

There are five main types of endocarditis. The *rheumatic* type develops during the course of an attack of rheumatic fever and is usually heralded by an increase in severity of this disease, *i.e.*, more discomfort and a rise in fever. Precordial pain, increase in pulse rate, murmur and often a considerable dilatation of the heart appear later. *Acute bacterial* endocarditis is also usually a secondary affair complicating one of the acute infectious diseases. Its diagnosis is usually based upon the appearance or increase in the signs of sepsis (septicemia) and the finding of a positive blood culture, though cardiac symptoms are sometimes prominent also. Some of these cases are so rapidly fatal as to have earned the appellation "malignant endocarditis." Then there are the cases of *subacute bacterial* endocarditis in which the patient with a preexisting valvular lesion experiences a reinfection of the endocardium

from an infectious process in the teeth, tonsils, middle ear, or other focus; Okell and Elliott (1935) showed how very frequently the nonhemolytic streptococcus of the *viridans* type, the organism most often involved in these cases, enters the blood stream from septic mouths. Middleton and Burke (1939) stressed the point that rheumatic valvulitis and congenital cardiac lesions are the most common precursors of this form of endocarditis. The disease runs an obscure febrile course until a murmur of growing intensity is detected, or petechiae on the extremities and visible mucous membranes and signs of splenic or kidney infarction make their appearance. Willius (1944) said that the occurrence of Osler's nodes—small painful nodules occurring either intracutaneously or subcutaneously as the result of minute bacterial emboli in the superficial terminal vessels in the pads of the fingers or toes—is pathognomonic of this affection. Christian (1941) said that if malaise and fever, joint or muscle pains, nausea or loss of appetite appear in an individual, usually a youth or young adult known or found to have chronic valvular or congenital disease of the heart, and persist for more than one week without the development of evidence of other definite disease, the probability of subacute bacterial endocarditis is great. Positive blood cultures are easy to obtain and assist in making an early diagnosis. Death is usually caused by cerebral embolism. *Mycotic* endocarditis is an extremely rarely encountered entity; Beamer *et al.* (1945), in reporting 2 cases of their own, brought the total number of reported cases caused by higher bacteria, yeasts or fungi up to 12. And finally there is the type of *nonbacterial* endocarditis, which is apparently comprised in the "atypical verrucous endocarditis" of Libman and Sacks, and the "thrombotic endocarditis" which Gross and Friedberg (1936) studied.

I believe that Matthew Baillie (1761–1823) was the first to describe endocarditis.

THERAPY

In all forms of endocarditis the patient must be kept absolutely quiet, to which end the use of the ice-bag, or in the asthenic individual hot applications, over the precordium is indicated; opiates should be used if pain and restlessness are severe. In the rheumatic type of the disease salicylates have no effect upon the endocardial process. Acute bacterial (malignant) endocarditis is best treated as a case of sepsis, the symptoms of which, indeed, usually dominate the picture; fever therapy seems to be of adjuvant importance in the gonococcal cases. In subacute bacterial endocarditis, in which spontaneous recovery occurs only in approximately 1 per cent of cases, the therapeutic outlook has been considerably brightened by the recent reports of successful employment of penicillin.

Penicillin.—Dawson and Hunter (1945) reported that of 20 patients treated with penicillin, 14 were in excellent general health and had been free from all evidence of infection for at least three months after treatment was stopped; 1 additional patient was in excellent health and had been free from all evidence of infection for four weeks. In an addendum to this report apparently successful termination of the disease was said to have been accomplished in 6 of 7 additional patients. Heparin (see below) was employed as an adjuvant to penicillin in the majority of the patients of Dawson and Hunter. Loewe (1945) has reported the treatment of 54 patients with penicillin and heparin and has stated that therapy was successful in 40, or 74 per cent. In 3 of Loewe's 14 patients (26 per cent) who were recorded as treatment failures the lack of re-

sponse was attributed to the refractoriness of the organisms; Dawson *et al.* (1944) had earlier drawn attention to the advisability of determining the sensitivity of the infecting strains in each case as a guide to appropriate therapy since the degree of sensitivity does not correspond with the cultural or serological properties of the strain. Loewe finds that in general the causative agents in subacute bacterial endocarditis are inhibited by penicillin within the dilutions of 0.007 to 0.5 Oxford units per cubic centimeter of test broth; under these circumstances, daily dosage of penicillin varies from 40,000 to 1,000,000 units, total individual unitage ranging in his experience between 867,000 and 48,930,000 units. As their experience accumulated, Dawson and Hunter established 200,000 units daily for three weeks as a standard regimen; however, in 3 instances signs of infection recurred when treatment was discontinued and only 1 of the 3 cases responded satisfactorily when the daily dosage was increased to 300,000 to 500,000 units. Dawson and Hunter are accumulating data on the relationship between *in vitro* sensitivity of the strain and the penicillin blood levels necessary to effect sterilization of the blood stream, and it is hoped that their studies will provide information of practical value.

Sulfonamides.—Lichtman (1943) reported the following results collected from the literature and the experience of the staff at Mount Sinai Hospital in New York: (*a*) of 489 cases treated by sulfonamides, 4 per cent recovered; (*b*) of 109 heparinized patients, 6.5 per cent recovered; (*c*) of 61 patients treated with artificial fever therapy, 6.5 per cent recovered; and (*d*) of 215 patients treated by sulfonamides supplemented by heparin or fever therapy, 8.5 per cent recovered. In reviewing the subject of the therapy of subacute bacterial endocarditis before the appearance of the favorable penicillin reports discussed in the section above, Willius (1945) stated his feeling that since occasional cures seem to result from the use of the sulfonamides their trial is always justified. For methods of sulfonamide and fever therapy see the Index.

Heparin.—This agent, which is used in the attempt to prevent further thrombotic deposition on the surface of vegetations, was formerly given by continuous intravenous drip according to the method of Kelson and White (1939). But this method was expensive and cumbersome, reactions occurred frequently, and deaths were attributed to the measure by a number of observers, though one should certainly note Kelson's (1945) statement that the frequency of cerebral deaths had not been increased in his patients under this type of heparin therapy. However, the newer method of subcutaneous administration of the heparin, devised by Loewe and Rosenblatt (1944), is considered by nearly everyone to be much safer than the intravenous method; it was employed by both Loewe and Dawson and Hunter in the combined penicillin-heparin series of cases discussed above. The Loewe-Rosenblatt heparin preparation comprises a mixture having the following ingredients: heparin, epinephrine, ephedrine, chlorbutanol, eucupin, and the Pitkin menstruum which contains gelatin, dextrose, acetic acid and distilled water. The preparation of this mixture for subcutaneous administration is a delicate and intricate procedure and cannot be described here. Indeed, it seems to me that the whole matter of heparin inclusion is still so much in the experimental stage as to warrant the average man in waiting a while before he employs this measure. Even Dawson and Hunter (1945), who heparinized most of their patients while treating them with penicillin, took occasion to point out that several of them had done just as well without this anticoagulant therapy and to state

their feeling that further experience in a considerable series of cases treated with and without heparin will be necessary before an opinion can be expressed as to its value.

Other Agents.—Osgood (1942) used 0.8 mg. per pound (0.5 Kg.) of neoarsphenamine, giving one such unit dose every four hours for the first day for 4 doses and then every eight hours for 3 doses each subsequent day for the duration of the course—courses of three to six days alternated with rest periods of about the same length. In the 4 cases treated either with neoarsphenamine or neoarsphenamine plus the sulfonamides blood cultures became negative and symptoms of the disease were absent for eight to sixteen months at the time of the report, but Katz and Elek (1944) used intensive mapharsen therapy in 2 cases with negative results. Berghoff *et al.* (1944) felt that the combination of sulfonamide, thiamine chloride intravenously and blood transfusions definitely improves the clinical picture temporarily, but that cures are not obtained. In a case caused by *Staphylococcus aureus*, Martin and Thomas (1943) employed injection of staphylococcus antitoxin; the patient recovered.

Surgery.—In Lichtman's review of a large number of cases (see above) surgical ligation performed on patients with patent ductus arteriosus complicated by subacute bacterial endocarditis produced the highest percentage of recoveries, but this is a cardiac anomaly which occurs in only a minor number of these patients. Polowe (1939) reported that splenectomy, introduced by Riesman, had been used in 4 cases proved by blood culture; 1 of the patients recovered; in 12 unproved cases it was the impression of most of the attending physicians that the patients had benefited from the procedure, and 2 seem to have recovered.

ACUTE MYOCARDITIS

Except for the relatively rare "acute isolated myocarditis," an entity which Saphir (1942) reviewed authoritatively several years ago, acute myocarditis is always secondary to one of the acute infectious diseases, being particularly prone to occur during or after an attack of rheumatic fever, influenza, scarlet fever, typhoid fever, diphtheria (especially if antitoxin is too long delayed or given in too small doses), or sepsis. There is usually a decrease in blood pressure with an increase in heart rate and the appearance of some sort of irregularity, though it must be admitted that the diagnosis of myocarditis is notoriously difficult to make; in diphtheria, bradycardia occasionally occurs and is almost invariably fatal. When acute heart failure makes its appearance the symptoms are the same as those of heart failure from any other cause. Nine of the 60 children in the series of Saphir *et al.* (1944) died suddenly.

THERAPY

The factor of greatest importance in the treatment of acute myocarditis is absolute rest. Not only should rest be enforced in all known cases, but in suspected cases as well, *i.e.*, in all attacks of rheumatic fever and the other acute infectious diseases listed above, the patient should not only be kept in bed but must lie quietly in the bed. In rheumatic cases in children, Taussig (1935) advocated the use of considerable doses of sedatives: phenobarbital (luminal), $\frac{1}{2}$ to 1 grain (0.03–0.06 Gm.) three times daily, or codeine, $\frac{1}{4}$ to $\frac{1}{2}$

grain (0.015–0.03 Gm.) twice or thrice daily or even every four hours if necessary.

During the course of acute myocarditis in rheumatic cases drugs other than the salicylates and the sedatives are usually of little value. Most physicians look upon digitalis as a dangerous drug here because of its tendency to accelerate an already established heart block. The drugs which ordinarily whip up heart action—caffeine, metrazol, coramine, epinephrine (adrenalin)—are often recommended and probably freely used, but it seems to me that in the very nature of things they are contraindicated. We have no effective medication in the heart failure of acute myocarditis and had as well admit it. In some instances the degree of anoxemia will indicate resort to oxygen, or the inability to take sufficient fluids and food by mouth will make it advisable to give dextrose in Locke's solution intravenously. In other instances venesection may relieve the right side of the heart of its load in time to be life-saving. Or sponging to quiet the patient may be absolutely the therapy of choice. In short, meet the indications as well as they can be met with woefully ineffective nonspecific measures.

Following the subsidence of active symptoms the patient is not to be allowed to rise suddenly from bed and resume the ordinary rounds of play or duty. Strength-testing by daily increases in pillow-propping is mandatory, and even after the patient is got gradually out of bed, the return to full activity, if this will ever be permissible again at all, must be accomplished with extreme slowness. The schedule below, which Taussig employed in the management of children convalescing from acute rheumatic myocarditis, will indicate what is meant.

1st month	1st two weeks	Up in a chair two hours in P.M.
	2nd two weeks	Up in a chair two hours in P.M. Walking to bathroom.
2nd month	1st two weeks	Up in a chair two hours in A.M. and P.M. Walking to bathroom.
	2nd two weeks	Up 10 A.M. to 1 P.M. and 3 to 5 P.M. This generally includes being up at the table for the noon meal.
3rd month	1st two weeks	Up 10 A.M. to 1 P.M. and 3 to 6 P.M.
	2nd two weeks	Up 10 A.M. Out-of-doors 11 A.M. to 12 noon. Lunch 12.30 P.M. Bed 1 to 3 P.M. Up 3 to 6 P.M.
4th month	1st two weeks	Up 10 A.M. Out-of-doors one to two hours A.M. and P.M. Two hours' rest in P.M. Bed 6 P.M.
	2nd two weeks	Up 9 A.M. Two hours' P.M. rest. Bed 6 P.M.
5th month	1st two weeks	Up 7.45 A.M. Two hours' P.M. rest. Bed 6 P.M.
	2nd two weeks	Up 7.45 A.M. School in A.M. ($\frac{1}{2}$ day). Two hours' P.M. rest. Bed 7 P.M.

CHRONIC MYOCARDITIS

(See *Chronic Nonvalvular Heart Disease*)

ARRHYTHMIAS NOT OF PRIMARY THERAPEUTIC INTEREST

There are properly three groups of cardiac irregularities: first, those which might be called "normal" without too great impropriety; second, those which are entirely secondary to some other underlying pathologic process; and third,

those which must be combated upon the basis of their own independent existence. Obviously, in a book such as this, mere listing of the entities in the first two groups must suffice so that detailed attention may be given to the last, or therapeutically important, group. In *sinus arrhythmia*, the heart rate gradually accelerates and retards usually synchronously with the phases of respiration; this occurs in all infants, many children and some adults, and disappears temporarily whenever the heart rate is increased in normal tachycardia; it appears occasionally during digitalis therapy and frequently as recovery from normal tachycardia takes place. *Sinus* or *normal tachycardia* is the acceleration in regular rate which occurs in hyperthyroidism, fever, exercise, shock, anemia, etc.; the treatment is that of the underlying condition; Barker *et al.* (1943) used quinidine in 5 cases and found that the rate was either not affected or slightly increased and in one patient a transient right bundle branch block occurred two hours after administration of the drug upon two separate occasions; in a well-controlled small series of cases having no apparent etiological basis, Waldman and Moskowitz (1944) aborted the attack by the intramuscular injection of 2 cc. (1 mg.) of prostigmin methylsulfate, and they found the prophylactic oral use of prostigmin bromide tablets (15 mg.) four times daily effective in preventing recurrence. The rare paroxysmal ventricular tachycardia, unlike the auricular form of tachycardia, is practically always a mere intercurrent affair in grave organic heart disease; it does respond very well, however, to quinidine therapy though the drug must sometimes be given intravenously; potassium chloride and magnesium sulfate have also been used but Williams and Ellis (1943) felt it not yet possible to evaluate their worth. In *normal bradycardia* the impulse is transmitted regularly but excessively slowly; this slow, regular rate is apparently normal for some individuals, but it also occurs in others during jaundice and in some of the deficiency states and at times during recovery from fever, and it must always be differentiated from true heart block. *Sinus pause* is the term used to indicate the occasional complete skipping of an entire beat which occurs now and then in healthy individuals—according to Levine (1936), under such diverse stresses as prolonged standing, a hot room, sudden twisting of the neck, the prick of a needle, the sight of blood, etc. The heart blocks which occur frequently in coronary and hypertensive disease, often during the course of diphtheria and rheumatic fever, occasionally in syphilitic cardiovascular disease, and very frequently during digitalis therapy, are: sino-auricular block, in which an impulse failing to leave the node of origin provides a pause between beats of twice the usual duration (this is very rare and in its most severe form is called auricular standstill); first degree block, an increase in conduction time between auricles and ventricles, usually detectable only with the electrocardiograph; second degree or partial block, in which, due to failure of some of the impulses to reach the ventricles, the auricles and ventricles beat in a rhythm of 2 to 1, 3 to 1, and so on; and bundle branch block, an electrocardiographically demonstrable delay or block of an impulse in one of the branches of the bundle of His. *Ventricular fibrillation*, for which there is no effective treatment, is practically always only a terminal event. *Pulsus alternans* is not a true arrhythmia but an alternation in force of the regular beats; the treatment is that of the underlying heart disease.

AURICULAR FIBRILLATION AND FLUTTER IN OTHERWISE NORMAL HEARTS

Auricular fibrillation is probably due to a self-perpetuating ring of excitation—"circus movement"—about the mouth of the superior vena cava, the auricles being maintained in rapid fibrillary contractions, to only a small number of which the ventricles respond. The pulse is extremely irregular in rate and unequal in force, and the count at the wrist, though usually high, is often less than at the apex due to the failure of some of the weak ventricular contractions to open the valves or initiate the wave; in rare instances the "pulse deficit" may be so great as to produce a rate at the wrist lower than normal. In auricular flutter the circus movement is slower than in fibrillation and it is responded to by the ventricles at a regular rate and in a definite ratio; *i.e.*, the relationship of ventricular-auricular impulses will be 1 to 2 or 3 or 4. Flutter is detectable only through study of the electrocardiogram.

Both of these arrhythmias, but especially fibrillation, have long been known frequently to complicate congestive heart failure from the usual causes, and likewise to appear not infrequently in advanced thyrotoxicosis. In recent years it has also been recognized that they may occur in a heart otherwise apparently entirely normal. In these instances palpitation is the most common symptom, pain the rarest; sometimes there is breathlessness, pallor, vertigo and nausea. Usually the paroxysms do not last longer than a week, but rarely an attack has persisted as long as a year and then terminated spontaneously. During the attack of fibrillation exercise increases both the rate and irregularity of the contractions. In Brill's (1937) case severe congestive failure appeared but entirely cleared up upon cessation of the arrhythmia. Most of the patients are at or past middle age when their first attack is experienced; frequency of paroxysms is variable but tends to diminish with the passage of time; the studies of Orgain *et al.* (1936), and Willius and Dry (1941), indicated that the prognosis for life and for the maintenance of cardiac function is usually excellent.

THERAPY

The treatment of these arrhythmias when they complicate congestive failure from other causes is usually quite secondary to treatment of the failure itself; *i.e.*, when all that is possible has been accomplished by the use of digitalis, the advisability of using quinidine must be separately weighed in each case—the matter is discussed in detail under Congestive Heart Failure. At present we are concerned only with fibrillation or flutter in otherwise normal hearts; *i.e.*, in postoperative cases of thyrotoxicosis in which spontaneous return to normal rhythm has not occurred, and in individuals who experience such paroxysms as above described. In a fibrillation of this sort digitalis is not regularly of value and quinidine is the drug of choice. It was a patient with paroxysmal fibrillation who first brought to Wenckebach's attention, in 1912, the use of quinine in the malady; Frey's investigations later caused the substitution of quinidine sulfate for the older drug. Quinidine is rather consistently effective, and increasing experience has shown that serious reactions are of infrequent occurrence in patients whose hearts are normal except for the arrhythmia. However, there is not always need to use the drug in these cases, since most of the paroxysmal attacks suddenly terminate spontaneously in a few days. The following symptoms of quinine intoxication are those most usually seen (Kohn and Levine, 1935): nausea, vomiting, epigastric distress, diarrhea, headache,

palpitation, tinnitus, apprehension, mental depression, flushing, sweating, syncope; disturbances of vision, extreme excitement and fever are of much rarer occurrence. Papular, petechial and scarlatinal rashes, and urticaria and inflammatory edema of the face have been reported. The more serious reactions, rare and usually occurring only in individuals with grave organic heart disease, are (*a*) sudden ventricular fibrillation and heart failure; (*b*) sudden death with respiratory failure, a type of effect reproducible in laboratory animals; (*c*) embolism—it is interesting to note that after a period in which we were somewhat in doubt as to the increased incidence of this phenomenon under quinidine's influence, Kohn and Levine's (1935) reexamination of the evidence reaffirmed earlier statements that the drug does tend to cause this accident to occur through suddenly restoring normal rhythm; more recently still, however, Smith and Boland (1939) expressed themselves as very skeptical of this.

Perhaps the most usual method of employing the drug in such cardiac-normal individuals as we are considering here is that described by Brill (1937) who gives a test dose of 3 grains (0.2 Gm.)—which alone was enough to arrest the paroxysm in one of his cases—and if there are no untoward effects in six to twelve hours, begins administration of 5 to 6 grains (0.3–0.4 Gm.) at four- to six-hour intervals until normal rhythm is restored or the appearance of toxic symptoms causes discontinuance. However, in using the drug following digitalis, when auricular fibrillation has complicated preexisting heart disease, recent experience has shown that a more intensive type of therapy is often more effective. A dosage scheme of this type, as described by White and Glendy (1936), is: after the test dose of 3 grains (0.2 Gm.), give 6 grains (0.4 Gm.) every two hours for 5 doses; if arrhythmia persists after these 30 grains (2 Gm.) have been given, 1 or 2 more doses may be cautiously given, or the program may be repeated on the following day. Sturnick *et al.* (1943) offered the following formula for a quinidine preparation suitable for parenteral use:

	Gm. or cc.
Quinidine hydrochloride	15
Antipyrine	15
Urea	20
Water to make	100

Of this mixture, which contains 0.15 Gm. of quinidine per cubic centimeter, they injected 3 to 4 cc. intramuscularly and repeated at intervals of one-half to four hours as indicated; a disadvantage is that sterilization by passage of the mixture through a Berkefeld filter is required. Quinidine is rapidly excreted and cumulative effects need not be feared, but patients receiving these large doses should be in bed under close supervision and should if possible have an electrocardiogram made before the first, third and fifth doses. White and Glendy considered that severe symptoms of cinchonism, tachycardia of over 150, or intraventricular block evidenced in the electrocardiogram, demand omission of the drug.

Willius (1939) said that it has become customary at the Mayo Clinic to give 1/60 grain (0.001 Gm.) of strychnine sulfate three times daily as supplementary medication if quinidine alone has not restored normal rhythm in three days. Wolff (1943) obtained better results in some cases through preliminary digitalization even if there were no underlying cardiopathy requiring the use of the drug.

For prevention of recurrence of auricular fibrillation, Brill used 3 to 6 grains (0.2–0.4 Gm.) once a day, but White and Glendy sometimes used such dosage as often as four times daily (even at three-hour intervals in some instances) for long periods of time; Gold (1940) also found the larger dosage preferable, sometimes building up to as high as 40 or 50 grains daily. Messeloff (1939) felt that practically adult dosage may be safely administered to children; his series of 12 children so treated ranged in age from six to fourteen years.

In auricular flutter it is the consensus that full digitalization should be preferred to the use of quinidine; the flutter is often converted into fibrillation which in turn ceases when digitalis administration is stopped. If digitalis fails then quinidine is to be tried.

PAROXYSMAL AURICULAR TACHYCARDIA

In this disturbance the patient becomes aware of a sudden great increase in the heart rate usually to from 120 to 180 beats per minute. The rhythm is regular and the rate is not decreased during rest. Such a paroxysm may persist for hours or even for many days, and the attacks may recur frequently during weeks, months, or years. Individuals without demonstrable cardiac pathology are just as liable to these paroxysms as are the victims of heart disease; the young are more often affected than the old. Hubbard (1941) reported 9 cases in infants under one year, and Weyler and Dustin (1942) the interesting case of a patient who presented this arrhythmia throughout the latter part of four pregnancies over a five-year period. The attacks terminate just as suddenly as they begin, and in most instances without having caused any disturbance other than distress and palpitation; in rare instances, however, there are associated neurogenic symptoms such as polyuria, sweating and dilatation of the vessels of the skin. Mild symptoms of transient congestion have been occasionally recorded. Some men are beginning to be interested in the possibility of an allergic origin of paroxysmal auricular tachycardia.

THERAPY

Mechanical Measures.—Pressure on the carotid sinus to induce arresting vagal stimuli often dramatically stops such an attack; Gold (1940) said the measure succeeds in about half the instances. Firm pressure is made over the carotid artery below the angle of the jaw and sustained for ten to fifty seconds; pressure should not be made upon both sides at once. Firm pressure over the eyeball is also often effective but it is painful. There are individuals who can stop an attack by indirect stimulation of the inhibitory mechanism, such as by deep breathing or holding the breath, vomiting, swallowing a hard bolus of food, or by assuming various postures.

Acetyl-β-Methylcholin (Mecholyl).—Starr (1936) introduced the use of this drug, which causes effects analogous to vagal stimulation. The attack was quickly terminated in 88 per cent of 75 instances in 37 patients. In 20 per cent of the instances carotid pressure was effective during the period of the drug's action though it had failed before. Mecholyl is given subcutaneously in dosage varying, according to age and weight of the patient, from $\frac{1}{6}$ to 1 grain (10–60

mg.). The injection is followed by a sudden sensation of warmth in the face, hyperpnea, sweating and salivation, and sometimes a sense of tightness across the chest. Morgan (1943) gave a preliminary injection of morphine to lessen the perception of these disturbing symptoms. The patient should be supine when injected. In some instances of failure, repetition of the same or a larger dose after half an hour may bring success; Gold (1940) gave as much as 1 grain (60 mg.) at one time intramuscularly, but the drug should never be given intravenously. Walsh and Sprague (1940) used 5-mg. doses in a child of five years. One can add to the effect by vigorously massaging the site of injection. Nausea and vomiting are perhaps the first symptoms of overdosage. An asthmatic attack seems to be precipitated in susceptible individuals and momentary heart block has also been noted in a few instances; coronary disease absolutely contraindicates the use of mecholyl. Starr found that atropine sulfate, 1/50 grain (0.0012 Gm.) intravenously, terminates any of these reactions almost at once. Morgan (1943) said he has a blood pressure cuff in place ready to prevent further absorption if necessary. It is felt that mecholyl is less effective when patients have been receiving quinidine or digitalis, and that in any case it is drastic therapy not to be employed unless other measures have failed.

Quinidine.—This drug is much used in combating the paroxysms; dosage, reactions, etc., are considered under Auricular Fibrillation; failures occur perhaps as often as successes. In the attempt to prevent recurrences, Gold (1940) preferred digitalis (see below) to quinidine.

Emetics.—Weiss and Sprague (1937) used the syrup of ipecac in 14 cases, successfully in each instance; this is an indirect method of stimulating the vagus. Ideally, a dose of 1 to 2 drachms (4–16 cc.) was given initially and repeated in the same or a larger dose if neither vomiting nor the desired effect was produced in forty-five minutes; practically, however, it seems to have been necessary to develop the dosage, number of doses and time intervals separately for each patient. Gold (1940) seemed to have a high opinion of ipecac and said also that not infrequently 1/20 grain (0.003 Gm.) of apomorphine hydrochloride will accomplish the same thing.

Digitalis.—Failure usually results from the use of this drug to stop a paroxysm. However, a number of years ago Levine and Blotner presented 4 cases in which keeping the patient digitalized (beginning with full doses and finally employing maintenance doses of approximately 2 grains of leaves, 0.13 Gm., per day) was effective in preventing recurrence in individuals prone to have many attacks during a year. This is a small number of cases, but it is suggestive that the failure of most workers to get satisfactory results may be due to their small dosage of the drug; in his book, Levine (1945) reaffirmed this position. Gold (1940) also felt that digitalization, with perhaps even double Levine's dosage, is the most effective safeguard against recurrences. Tandowsky (1945) used cedilanid (lanatoside C) intravenously to stop the attack in 8 cases and then continued the administration by mouth, reducing the frequency of attacks from 4.2 in a twelve-month period to 0.37 in a fifteen-month period; the amount of the drug given intravenously to stop the attack was 1.6 mg. and the daily oral dose exceeded 0.5 mg. in only one of the cases. Hubbard (1941) used digitalis with satisfaction in most of his infants under one year: digifoline intramuscularly in dosage of 0.05 to 0.1 Gm.

Other Measures.—Boyd and Scherf (1943) injected 15 to 20 cc. of a 20 per cent solution of magnesium sulfate intravenously in about thirty seconds

with success in all of their 8 cases, but they said they would hesitate to employ the drug when marked myocardial damage was obvious or if there were marked intraventricular conduction disturbances or gallop rhythm present. Boyd (1942) reported the termination of attacks through the intravenous administration of 1 cc. of the commercial ampule preparation of metrazol. A good many years ago injection or removal of the stellate ganglion was suggested in patients stubbornly refractory to other methods of treatment; Schwab and Willis (1942) found records of the employment of this treatment in 11 cases with some improvement apparently being effected in all.

EXTRASYSTOLE

Premature systoles occur at some time in the life of most individuals; the phlegmatic often do not notice them at all, but in the nervous individual the abnormality is quite annoying. The heart usually "thumps" or "turns over" and then there is a long pause before the next beat occurs; this compensatory pause, due to the occurrence of an extrasystole during the period of diastole, may be felt at the wrist and is usually equal in length to the time of two normal beats. These premature contractions, when they occur over a long period of time, may become a serious matter in that the patient often loses appetite and the ability to sleep, and may even suffer a considerable impairment in general health, because of nervous worry. If unassociated with any demonstrable cardiac pathology, as is usually the case, extrasystole is quite without direct significance, but since this phenomenon sometimes heralds the beginning of serious heart maladies it is always incumbent upon the practitioner to make a thorough examination of his patient before pronouncing the matter of no moment. Some men are thinking of the possibility of an allergic origin in some instances of extrasystole.

THERAPY

It is one thing to tell a patient that his heart is quite all right and another to get him to believe it in face of the heavings of which he is aware in his chest. Many individuals are quite capable of believing, during the busy daylight hours, that what the physician tells them is true, but when night comes and they lie bedfellows with their misbehaving hearts apprehension grips them hard. It is wise not to overlook the advantage of reestablishing the habit of sleep by the use of sedatives or hypnotics for a while (see Insomnia).

Quinidine and Strychnine.—The methods of employing quinidine are detailed in Paroxysmal Auricular Fibrillation. The drug is often helpful. Many years ago, Wenckebach, the late authority on arrhythmias, wrote: "I have found strychnine in small doses helpful in cases of extrasystole in otherwise normal as well as in diseased hearts, but very often it did not act strongly enough, or it lost its action very soon. In these last cases I tried the combination of quinine and strychnine and found that this form of treatment had complete success in the great majority of my cases. I have given from 0.3 to 0.4 Gm. (5 to 6 grains) of quinine daily, plus 2 or 3 mg. (1/30–1/20 grain) of strychnine through periods of ten days. My experience with this treatment since the year 1915 has been so favorable that I am convinced that whoever

will try it will come to the same conclusion." The rationale of strychnine's use here is certainly difficult to understand; nevertheless, Carter and Traut (1935), using the more modern quinidine instead of quinine, also reported better results when employing strychnine at the same time.

Papaverine.—Elek and Katz (1942) reported a small series of cases in which 3 grains (0.2 Gm.) of this drug, taken orally four or five times daily, was highly effective.

Potassium Acetate.—Sampson and Anderson (1936) found this salt, in 25 per cent solution by mouth, effective in about half of the cases of extrasystole or tachycardia in which they employed it, most of the failures, however, being in cases such as we are considering here (*i.e.*, those having no apparent organic basis). The usual method is to attempt to prevent extrasystole during the night by administration of 45 grains (3 Gm.) of the salt upon retiring, and repeating this or a larger dose after three hours if the first has been ineffective. Sampson looked upon advanced nephritis as a contraindication to the use of the drug. He saw 4 paradoxical instances in which the administration of potassium either increased the extrasystole or actually produced paroxysmal ventricular tachycardia.

Aminophylline.—It has been reported that coronary dilators will occasionally abolish this arrhythmia even in the absence of any cardiac abnormality. These drugs have the advantage of at least being free from danger; see Index for methods.

HEART BLOCK

(*Adams-Stokes Syndrome*)

Complete heart block, with its associated symptoms, is a definite symptomatic entity, the block being due to arteriosclerotic, syphilitic, tuberculous, rheumatic, or adipose changes in the conduction tract; it should be noted, however, that at autopsy some cases have been found to exhibit no lesions of the bundle. The victims of this disease usually have a pulse rate of between 25 and 40 and suffer fainting spells which often occur at such frequent intervals that the patient is in almost constant anguish. The syndrome usually makes its appearance in individuals past middle age, and in its milder grades is not incompatible with a normal duration of life, especially in those who are fortunate enough to live in partial retirement, but from one of the syncopal attacks the patient finally does not recover.

This disease was described by Robert Adams, in 1826, and shortly thereafter by William Stokes—both leading members of the great Dublin school of the first half of the nineteenth century—but Flaxman's (1937) interesting historical study revealed that descriptions had in fact been published before this time.

THERAPY

Atropine.—Atropine paralyzes the vagus endings and should therefore release the heart from vagal inhibition, but as a matter of fact we do not as yet definitely know to what extent the ventricles are under this control. It is known, however, that vagus tone as a whole in man is greatest under thirty years and markedly decreases after fifty—which fact in itself would be quite sufficient to explain the usual failure to quicken the heart in Adams-Stokes

disease, most of whose victims are elderly. The drug is used in large doses, 1/20 to 1/12 grain (0.003–0.005 Gm.), subcutaneously.

Epinephrine.—Epinephrine is used because of its well-known ability to stimulate the sympathetic innervation of the heart and thus to cause an increase in rate. Dosage is 0.3 to 0.6 cc. of the usual 1/1000 solution, subcutaneously, never intravenously. Though admitting, in agreement with others, that epinephrine is by no means always successful in combating attacks, Gilchrist (1934), who had apparently closely studied this disease, stated that no other drug has proved more effective, and he therefore felt that since we cannot as yet predetermine which patients will and which will not benefit, this drug should be given a trial in the treatment of all cases. Levine (1942) said that when many attacks occur during a day, as sometimes happens in acute coronary thrombosis, it may be necessary to give injections every two hours for a day or so.

In dire emergency the drug may be injected intracardially. Easby *et al.* (1935) briefly described the method: "Select the fourth intercostal space, at the upper border of the fifth rib, close to the sternum. Use iodine. Take a long, thin needle, 6 to 10 cm. in length. Insert as far as the posterior sternal margin, incline slightly in a mesial direction, push in 4 to 5 cm. After some blood is aspirated, slowly make the injection of 1 cc. adrenalin. Movements of needle due to cardiac contractions are favorable. One reaches the right ventricle by this method. By this site injury of internal mammary artery and pleura is avoided. The fine needles largely preclude injury of coronary vessels or conducting system."

Schwartz and Jezer (1932) considered that epinephrine may be life-saving where the seizures are due to ventricular slowing (as is always the case in true Adams-Stokes syndrome), but that it is contraindicated when they are the result of ventricular fibrillation; there is general concurrence in this opinion. Levine (1942) recorded a rare instance of the latter sort in which the number of attacks seemed to be lessened by constant quinidine administration.

Ephedrine Sulfate.—There have been several reports of success with this drug in a single or small series of cases but doubtless it has failed in many more unrecorded instances. Gilchrist believed it worth a trial in the attempt to lessen the incidence of seizures; it was successful in 4 of his 6 cases. Easby suggested that because of the drug's tendency to cause urinary retention in some individuals, the starting dose be only $\frac{1}{8}$ grain (0.008 Gm.); full dosage is $\frac{3}{8}$ to $\frac{1}{2}$ grain (0.024–0.03 Gm.), three or four times daily by mouth.

Barium Chloride.—This drug was introduced a number of years ago in the attempt to increase the irritability of the ventricles. Cohn and Levine obtained striking effects in their 3 patients, using $\frac{1}{2}$-grain (0.03 Gm.) doses three or four times daily by mouth. Such results have been had by others, but there has certainly been at least an equal number of failures; for example, Parsonnet and Hyman (1930) were unsuccessful in 8 consecutive cases, a large series as Adams-Stokes syndrome goes. The drug is now being used in somewhat larger doses than those originally employed—up to as high as 5 grains (0.3 Gm.) three times daily in some instances according to Gold (1940). In Gilchrist's experience these larger doses have not been harmful, but it may be worth noting that in Graham's (1934) case of accidental ingestion of an enormous amount of barium chloride, crystalline sodium sulfate in dosage of several teaspoonfuls by mouth proved an effective antidote.

Other Drugs.—Upon the whole, the use of thyroid substance or thyroxin,

which causes tachycardia in the normal individual, has been very disappointing in this malady. However, Easby *et al.* (1935) reported favorably, using ½ to 3 grains (0.03–0.2 Gm.) of thyroid extract daily, and Parker and Willius (1938) referred to its use still more recently. Vasodilators have been recommended to reduce peripheral circulatory resistance and thus aid the handicapped myocardium—such drugs as aminophylline and the nitrites, as used in angina pectoris. Lueth (1938) thought that metrazol was effective in 2 of his 4 cases, and Myres (1941) obtained symptomatic relief with it in both of his cases. Sigler (1939) found his 4 patients definitely improved by intravenous injections of 50 cc. of 50 per cent dextrose solution. Starling (1938) felt that the intravenous injection of 10 cc. of 5 per cent peptone which he used in his patient was beneficial; his report of the fifteen years' course of this case is very interesting.

CHRONIC NONVALVULAR HEART DISEASE

(*The Failing Heart of Middle Life, Myocardosis*)

A very large proportion of the patients in whom symptoms of cardiac derangement have developed after the age of forty may be classified under this present head. They have neither endocardial, pericardial, valvular nor coronary lesions, and their disability seems to depend entirely upon inefficiency of the muscle. The cases may be placed more or less satisfactorily in Christian's three groups: (*a*) Patients who at any age complain of great exhaustion or of palpitation following slight exertion. They do not have true dyspnea but experience uncomfortable sensations in connection with respiration, perhaps have some substernal distress, and are sensitive to pressure in the region of the apex, and their heart rate is easily accelerated. Examination reveals a normal heart, but with perhaps a few extrasystoles and a rather tapping pulse; there are no evidences of past or present edema or passive congestion. Usually an adequate cause for the condition can be found in antecedent infections, in debilitating diseases with a too short convalescent period, or in occupational overfatigue together with worry and loss of sleep. (*b*) Patients, usually past forty, in whom the chief departure from normal is in the size of the heart, hypertrophy often being very marked. Just what causes this hypertrophy, and why the hypertrophy should result in dysfunction, has never been satisfactorily explained. There may or may not be a soft to loud systolic murmur best heard at the apex, but it is important to bear in mind that the mitral insufficiency is the result, and not the cause, of the myocardial insufficiency. This cardiac enlargement would seem to mark the beginning of a train of events which practically always ends in cardiac decompensation. (*c*) Relatively uncommon are the patients with true chronic myocarditis. At autopsy there may be found small foci of perivascular infiltration with lymphocytes and plasma cells, or, far less frequently, a focal or a widespread fibrosis with definite evidence of injury to the muscle fibers. These chronic myocarditis cases are said to be indistinguishable clinically from those, above described, in which there is hypertrophy and no other change.

THERAPY

Myocardial Fatigue.—The practitioner who will assure patients with simple myocardial "fatigue," those described in group (*a*), that they have no heart

disease and are sure to get well renders a real service to mankind, for these patients form a large class of chronic invalids who burden their friends with their "weak" hearts; and all because an incorrect diagnosis was made in the beginning. Rest and reassurance, with a gradual return to full physical activity, is all that is needed in these cases; indeed, their easy curability is the chief mark by which they may be distinguished from cases of neurocirculatory asthenia, previously discussed. Christian says that these hearts, which are normal in size, sounds and function, offer the striking example of when digitalis should not be used, not that it is harmful but because it is not beneficial. Yet many of these patients are found to be entirely dependent upon daily doses of digitalis which would be inadequate if the drug were actually needed, or they may take it only when their heart is "bad," getting immediate relief—"all of which goes to show," says Christian, "that for such patients digitalis in such doses is not a cardiac medicine but one that works directly on the mind."

Hypertrophy and Chronic Myocarditis.—These cases, those described in (*b*) and (*c*) above, are said often to present very considerable diagnostic difficulties by reason of the fact that a regular rhythm is frequently maintained, but decompensation here, as in other types of heart failure, indicates digitalis—Christian has long been stoutly championing this viewpoint which has been substantially supported in recent years by the observations of Gavey and Parkinson (1940), Wood (1940) and Larson and Hallock (1940). For example, Gavey and Parkinson compared the drug's action in 65 cases of decompensation with normal rhythm and 30 cases with auricular fibrillation: 60 per cent beneficial results were obtained in the former and 70 per cent in the latter cases; Wood obtained a beneficial effect in 90 per cent, and Larson and Hallock in 70 per cent, of their smaller series of regular rhythm cases. For the details of digitalis therapy the discussion of congestive heart failure must be read.

In cases of cardiac enlargement, even though there be no signs or symptoms of decompensation, Christian uses digitalis continuously in amounts just short of toxicity and feels certain that there is no reason to fear deleterious effects from such therapy.

CONGESTIVE HEART FAILURE

This is the state of broken compensation in which the heart is no longer able to perform the amount of work necessary if the body as a whole is to maintain a condition of normal activity. When first seen, if the decompensation is severe, the patient is in bed, usually propped up on several pillows, has a depressed though anxious expression (perhaps even pronounced symptoms of mental disturbance), is breathing with difficulty, may or may not be cyanotic, and has a rapid and usually arrhythmic heart. Edema of the lower extremities is usually present, and perhaps even anasarca with fluid in the serous cavities. The liver is engorged, the kidneys congested, and the urine is scant and contains albumin and casts. Often there are râles at the lung bases and congestive cough and even hemoptysis; sometimes "cardiac asthma" and complaint of cardiac pain. Slight fever is not at all infrequent even in the absence of infectious processes.

When primary left ventricular failure has persisted for a time the right ventricle not infrequently participates in the failure also and the picture is of the rather conglomerate sort roughly sketched above, but primary left ventricular failure alone presents quite characteristic symptoms when it occurs as the result of excessive strain upon the left ventricle or deficiency in its contraction or the expulsion of its blood as in hypertensive cardiovascular disease, in aortic insufficiency of rheumatic or syphilitic origin and in coronary arteriosclerosis. Dyspnea, orthopnea, râles in the lungs, an anginal type of pain and frequent attacks of one or another sort of arrhythmia are the outstanding features. And then these patients are very likely to develop attacks of paroxysmal dyspnea which are frequently provoked in the night by bad dreams, or by an orthopnic patient slipping off his pillows, or perhaps as a result of distention of the abdomen from overeating; not infrequently such attacks eventuate in pulmonary edema. Oftentimes left ventricular failure begins slowly over a period of years and many patients who would profit by treatment for heart failure in its early stages merely complain of discomfort in bed at night unless propped up on several pillows, or a chronic bothersome cough, or some degree of effort angina, or some type of arrhythmia, and are treated merely for these single symptoms. There is another sort of left ventricular failure which occurs very suddenly as a result of massive myocardial infarction, but the symptoms which quickly supervene are those of peripheral circulatory failure and the treatment is that for shock and therefore does not concern us at this time.

In primary right ventricular failure, which is often in association with some obstructive situation or with mitral or congenital heart disease, dependent edema and signs and symptoms of engorgement of the abdominal organs and secondary congestive respiratory symptoms are usually the matters which chiefly attract the attention of the examiner. The right ventricle decompensates much more readily than the left but on the other hand it recompensates much more quickly and more frequently; by and large then the prognosis is much better in right than in left ventricular failure.

THERAPY

Rest.—Rest in bed is usually self-imposed in cases of severe failure, though it is astonishing how long individuals of indomitable will are sometimes able to keep on their feet; it is of course imperative if cure is to be accomplished that the patient be placed in bed even though he is able to repose there only in a sitting posture. This is by no means the same thing as saying that every patient with decompensation will show direct profit by being sent to bed, for the factors of arrhythmia, edema and congestion, and so on, are grave perpetuators of the broken-down state, but it does mean that, other things being equal, the patient who takes to his bed early and rests while he is in it, has the best chance of recovery, be his decompensation slight or great. However, as Levine (1940) pointed out, there are instances in which putting the patient to bed may cause a shift of some of the fluid from the dependent extremities, where it is relatively harmless, into the lungs, with the possibility of establishing serious congestion there before digitalis can begin moving the fluid to the kidneys. Harrison (1944), whose reviews regarding the abuse of rest in cardiovascular disease have been presented in some detail in Coronary Occlusion, feels that individuals with congestive heart failure should be allowed out of bed for several hours a day as soon as severe dyspnea at rest has subsided.

Individualization of treatment should therefore be the watchword here as everywhere!

To the end of providing complete rest, even though the patient be one of the minority whom it may seem desirable to keep up in a chair with the legs hanging down in the beginning, it is often advisable to employ sedatives (see Insomnia). Eggleston (1942) said that he frequently finds chloral hydrate a better sedative in these individuals than the barbiturates and that, if the patient can be got to take it, paraldehyde is the best of all. Sometimes the best sedative is an analgesic—morphine, dilaudid, codeine, demerol, for a few doses. Some patients are relieved by the ice-bag applied to the hypochondrium.

Diet and Fluids.—In the beginning of an attack of decompensation the patient will not be interested in food, but in a few days, especially after the use of sedatives and analgesics has been stopped, the matter of dietetics needs to be faced. Some physicians like to keep the patient on the radical Karell diet (a glassful of milk at 8 A.M., noon, 4 and 8 P.M., and no other food or fluid) as long as he will take it, which is usually no more than a few days, and then add small but frequent feedings of such substances as vegetable purées, lightly cooked red meats, chicken, fish, well-baked breads and well-cooked potatoes and green vegetables, rice, tapioca, custards and ice cream. All this may perhaps be summed up by saying, give the patient only milk in the beginning and thereafter small frequent feedings of a general diet. Of course in these vitamin-conscious days one should look into the possibility of a preceding deficiency and make such corrections by supplementary vitamin therapy as may be indicated. With a view to avoiding attacks of paroxysmal dyspnea in the night, Eggleston (1942) advised that special care be taken after midday to avoid overloading the gastro-intestinal tract with either food, fluid, or gas. Salt is usually reduced to the minimum in the diet and fluid often restricted to 1 quart (liter) per day, but it does not seem advisable to permit the patient to be excessively thirsty or have the discomfort of a dry mouth. Levine (1940) pointed out that when there has been excessive sweating, or if the nonprotein nitrogen in the blood is rising, it may be necessary to force fluids for a short period. I am not aware that anyone save himself has as yet adopted Schemm's (1942–1944) interesting proposal of a high fluid intake in the management of edema. If a patient with heart failure is obese most clinicians believe that some attempt should be made to reduce his weight.

Digitalis Indications and Effects.—The response of a decompensated heart with auricular fibrillation to digitalis is very spectacular. The pulse is decreased in rate and increased in volume; diuresis is established and edema decreases; dyspnea and cyanosis diminish—in short, compensation is reestablished and the patient's life is saved. In nonfibrillating cases, of the sort earlier described as "chronic nonvalvular heart disease," the reduction in rate is not so pronounced because the increase has not been as great, but the other evidences of powerful action are shown. I think that Levine's (1940) authoritative statement should be placed here *in toto:* "It must be borne in mind that digitalis is indicated in congestive heart failure whether the blood pressure is high or low, whether the rhythm is regular or grossly irregular, and whether the rate is rapid or slow. It is to be used in myocardial or in valvular disease, whether fever is or is not present, and whether the basal metabolism is normal or elevated. The results to be expected may differ under varying circumstances

but the indication for its use remains the same." The study of Blumgart and Altschule (1939) indicated that digitalis, in somewhat reduced dosage, may be safely employed for the correction of congestive failure in the presence of partial heart block. Erickson and Fahr (1945) treated 39 patients with clinically compensated but organically diseased hearts by giving them six 0.5 mg. tablets of cedilanid (lanatoside C) daily for two days and then one to two tablets on alternate days as a maintenance dose; the findings in this very interesting attempt to prevent decompensation through the use of a digitalis body convinced the observers that definite improvement in mechanical efficiency of the heart was effected in 87 per cent of the cases and that in the cases not so benefited the condition was at least not made worse by use of the drug.

Digitalization with the Leaf by Mouth.—Since Eggleston, in 1915, revolutionized digitalis administration by demonstrating that much larger doses of the drug could be safely used than had been the custom up to that time, it has become quite customary to employ the original Eggleston dosage for the 150-pound man, 22½ grains (1.5 Gm.) of leaf, as the average effective total dosage, portions of this total to be administered at intervals according to an arbitrary scheme. Many such schemes have been published; I have formerly filled my pages with them, but now I believe that nothing can serve the reader better than to state here the simple plan followed by Christian (1937) of Boston; for patients with marked decompensation not having received digitalis in any form within the past week, the initial dose should be 7½ grains (0.5 Gm.), to be repeated in four hours, and usually again four hours later, the patient thus receiving 22½ grains (1.5 Gm.) in the first eight-hour period. Thereafter, doses of 1½ to 3 grains (0.1–0.2 Gm.) may be given three times daily until therapeutic effect is achieved or evidences of toxicity appear. In this scheme the foregoing initial large doses should be increased for cases of greater severity and for very large patients. Conversely, for small patients these initial doses may be curtailed or abandoned. Abandonment of the large initial doses is particularly indicated when the patient previously has been getting digitalis in any considerable amount.

The above dosage scheme is designed for employment in acute fulminating failure where rapid digitalization in the matter of a few hours is imperatively necessary. In most patients, however, one may safely take two or three days instead of a few hours to induce the full therapeutic effects of the drug. In such cases it is frequently the practice to give only 3 grains (0.2 Gm.) three or four times daily until the desired effects are achieved. Indeed, Gold (1942) said that it is easily possible to digitalize a patient by giving him only 3 grains (0.2 Gm.) once daily if one is willing to wait long enough for the results. This amount is ordinarily looked upon as only maintenance dosage but Gold said that one can actually build up digitalis in the body with this type of administration if there has been no large accumulation of digitalis present to start with.

In the above it is assumed that a biologically standardized leaf in tablet, pill, or capsule form, will be used, but I certainly think that the assurance with which many clinicians speak of their dosage in terms of cat units is unjustified since there is plenty of evidence that the cat unit belongs in the laboratory and not at the bedside. Indeed, the *U. S. Pharmacopoeia* has changed its standard in each of the last three editions, but it still seems to me that the only bio-assay method that promises to be really reliable is that

in which the drug is actually assayed on the human being in the method which Gold and his associates are developing. Therefore, until this or some other method is so perfected as to assure us that any unit of digitalis is the exact equivalent of any other unit no matter from whom it is purchased, I feel that the best thing the practitioner can do is to learn what he can accomplish with the product of a given manufacturer, since at least he will have under such conditions reasonable assurance that this product will be of continuously uniform quality as it will likely be biologically assayed under the same laboratory conditions steadily. As a matter of fact when a man digitalizes his patient by a broken dosage method, as outlined above, he has rather good control of the situation and can usually adjust dosage to meet the conditions both with regard to the patient and the preparation of digitalis at hand. Significant deterioration of the leaf preparations when kept dry does not take place.

Modification of Dosage for Children.—Taussig (1935), at Johns Hopkins Hospital, offered the following dosage for a child weighing 50 pounds (22.7 Kg.): give 1½ grains (0.1 Gm.) as test dose; two hours later, 3 grains (0.2 Gm.); six hours later, 3 grains again; and six hours thereafter, 1½ grains. If not digitalized at the end of the twentieth hour, continue 1½-grain doses every six hours for 3 or 4 more doses provided there are no signs of toxicity, and then place the child on maintenance dosage. However Stewart (1942), of the Cornell Group, said his observations with Cohn were that body weight has nothing to do with the amount of digitalis required for therapeutic effect and that he therefore gives the same amount to children as to adults; questioned further with regard to this attitude he stated that the youngest patient he had so treated was a four-year-old child with auricular fibrillation to whom full adult dosage was given and therapeutic effect achieved without the induction of nausea and vomiting. Walsh and Sprague (1941) found that good responses to digitalis were obtained in only about one half of their 35 children with rheumatic heart disease, which seems to be about average experience. If it is desired to digitalize more slowly, give 1½ grains three times daily at six-hour intervals (8, 2 and 8 o'clock, or 10, 4 and 10 o'clock) for three days; fourth day, a dose in the morning and if necessary at night; thereafter maintenance dosage, which would probably be ⅚ grain (0.05 Gm.) daily, six days a week.

Digitalization with the Tincture by Mouth.—Biologically standardized tincture, which in the opinion of many observers is not quite so good as the leaf, may be substituted in dosage ten times as great; *i.e.*, 15 minims (1 cc.) of the tincture instead of 1½ grains (0.1 Gm.) of the leaf. Significant deterioration of the tincture does not take place if the bottle has been kept tightly closed. Prescribing a tincture in drop dosage is open to two serious objections: first, the droppers vary greatly in the amount of an alcoholic preparation they will deliver; and second, not all patients or their attendants at home are sufficiently disciplined to use a dropper with complete integrity. Perhaps the better way of prescribing a tincture (but why use it at all?) is in a bottle with a suitable vehicle to bring the 15 minims (1 cc.) dose up to 75 minims (5 cc.). A graduated vial prescribed with the medicine will then insure accuracy in dosage. In the following prescription the vehicle chosen is one containing no hydrochloric acid, which has given all vehicles their undeserved reputation of causing deterioration of the tincture, and contains about the same amount of alcohol as the tincture; it makes a mixture as little disagreeable as any. If the teaspoon the patient uses after he breaks the vial contains exactly 5 cc. he will still

obtain 1 cc. of tincture digitalis in each dose. If not, and he will only continue to use the same spoon, the error will be at least a constant one.

℞	Tincture of digitalis U.S.P.	℥xiiss	50.0
	Iso-alcoholic elixir (N.F. VII)	℥viij	250.0
	Label: 1 or more teaspoonfuls (5 cc.) as directed.		
	Dispense a ℥ss (15 cc.) measuring vial.		

Digitalization with the Newer Glycosides by Mouth.—Studies in recent years with the newly obtained crystalline glycosides obtained from both *Digitalis purpurea* and *D. lanata* indicate that we may be in a fair way of achieving the highly desired crystalline active principle which will not require biologic standardization. It seems to me that the use of these preparations is still best left to specialists who are in best position to make a thorough study of their potentialities, and I cite below some of the findings of such groups. *Digoxin:* Rose *et al.* (1942) found this agent to fulfill all the requirements of a satisfactory digitalis preparation when given orally in a group of 55 hospitalized and 33 ambulatory patients. The average therapeutic and toxic doses, as ascertained by rapid digitalization, were 3.75 and 6.0 mg. respectively. Earlier workers estimated that the amount required for maintenance was approximately one third of that necessary to produce full digitalization, but Rose *et al.* had 12 patients in a group of 24 who required 0.5 mg. or less and only 3 who required more than 1.0 mg. for adequate maintenance. The dosage finally recommended by these workers for rapid digitalization with the oral preparation was 1.5 mg. as an initial dose, to be followed by doses of 0.75 mg. at six-hour intervals until the desired effect is obtained, and thereafter a daily maintenance dose of 0.5 or 0.75 mg., to be varied by 0.25 mg. according to requirements. *Cedilanid:* Parsonnet and Bernstein (1943) employed this agent by mouth in 100 patients, 25 of whom had never taken digitalis. In 98 per cent of the group there was admirable response to the oral administration of cedilanid, the action beginning almost uniformly sooner than that of digitalis and disappearing more rapidly; they found also that once a maintenance dose was established this could be continued indefinitely provided the patient's condition was not altered by sudden overexertion or coronary failure. When the rapid and massive method of digitalization was used the total dose of cedilanid was approximately 10 to 15 tablets (5 to 7.5 mg.); the average maintenance dose was 1 to 3 tablets daily (0.5 to 1.5 mg.). These findings were substantially in confirmation of those earlier made by Fahr and La Due (1941) who found the dosage best suited to the majority of patients was an initial 15 tablets (0.25 mg. each) followed within twelve to twenty-four hours by 10 additional tablets given in single or divided doses. Fahr and La Due also found that some patients who could not tolerate digitalis leaf were able to take sufficient tentative cedilanid to effect relief. *Digilanid:* This agent theoretically should be the ideal one since it comprises a mixture in constant proportions of three "pure" crystalline glucosides obtained from *D. lanata*, and indeed according to Batterman *et al.* (1941), and Rimmerman (1945), it does satisfy the established criteria for a reliable potent digitalis preparation. Except when employing the agent intravenously in emergency cases (see under "Rapid Digitalization" below), Rimmerman found that slow digitalization of most of his patients could be satisfactorily accomplished by giving one tablet of 0.33 mg. three times daily. *Digitaline nativelle:* This agent is discussed under "Rapid Digitalization" below.

Digitalization with the Glycosides by Intramuscular Injection.—In an occasional case in which congestive vomiting is very severe in the beginning and there is some reason for not digitalizing the patient by an intravenous method (see below), the ampule preparation of digilanid may be satisfactorily used intramuscularly apparently, though not a great deal of experience has been had with this agent as yet; the dose is stated in N.N.R. (1944) to be 2 to 4 cc. daily, which would be the contents of 1 or 2 ampules. For this purpose the older glycosidal preparations—digalin, digifoline, digitan—in dosage recommended on the ampules, are much used but I do not know of any authoritative study showing these injectable preparations to be as reliable as the leaf; Eggleston (1940) said that he found very little occasion for using them.

Digitalis by Rectum.—Levy's studies of some years ago, indicating the feasibility of rectal administration of digitalis, have been amply confirmed. The older glycosidal preparations, digitan, digalin, digifoline, are given in the same dosage as would be used intramuscularly (see above), preceding the administration by a cleansing enema and washing the drug in with about 1 ounce (30 cc.) of saline solution. For convenience the total daily dose may be given at one time. There is also commercially available a suppository of digilanid containing 0.5 mg.; N.N.R. (1944) states the dose to be 1 or 2 suppositories daily. The tincture of digitalis may also be used, but the necessary dilution to avoid excessive irritation by the alcohol (4 cc. of tincture in 100 cc. of water) is likely to make the bulk too great for easy retention.

Rapid Digitalization.—When digitalis leaf is given by mouth, full effects are not obtained under twelve to twenty-four hours but beginning effects may be seen in two to four or five hours; thus a life-saving degree of digitalization is accomplished quite rapidly enough by oral administration in the vast majority of cases. In the occasional case where speedier action is thought necessary, there are now three methods of administration available:

Strophanthin (Ouabain) Intravenously: Crystallized ouabain, the glycoside obtained from *Strophanthus gratus*, is the preferred preparation in America; in England *S. kombe* is used and *S. emini* has been investigated. The commercial ampule contains the drug in buffered solution in hard glass, under which circumstances it is stable. Wyckoff and Goldring worked out the dosage at Bellevue Hospital a number of years ago: in patients having received no digitalis in the preceding two weeks, the initial dose is 1/120 grain (0.5 mg.); Eggleston (1940) advised that the dose be placed in 10 cc. of fluid and five to ten minutes be allowed for injection. Beginning effect is observable in a few minutes in average cases and full effect in about an hour. Most conservative men nowadays give only one dose or at most do not repeat the dose in less than twenty-four hours, but Wyckoff felt that in the presence of marked auricular fibrillation, where therapeutic effect can be easily noted, several subsequent doses of 1/600 grain (0.1 mg.) may be used at half-hour intervals after the initial large dose; Eggleston (1940) preferred one- to two-hour intervals if these subsequent doses are to be given. Of course the sole object of ouabain intravenous therapy is to save the life of the patient until peroral therapy may be begun, but just when to begin the oral therapy under these circumstances and how much of the drug to give have been important and not entirely settled questions. However, Batterman *et al.* (1940), also of the Bellevue group, showed that the following plan is feasible: (*a*) give simultaneously 1/120 grain (0.5 mg.) of ouabain intravenously and 10 grains (0.6 Gm.) of digitalis leaf by mouth (6 grains, 0.4 Gm., for those under 125 pounds edema-

free weight; 10 grains, 0.6 Gm., for weights between 125 and 175 pounds, 13 grains, 0.8 Gm., for weights above 175 pounds); (*b*) no further medication for twenty-four hours; (*c*) determine maintenance dosage by trial thereafter.

Cedilanid Intravenously.—La Due (1943) used this preparation intravenously for rapid digitalization in 83 patients, 62 with auricular fibrillation and 21 with regular sinus rhythm; the dose employed was 8 cc. of the ampule preparation containing 1.6 mg. In the vast majority of the patients the pulse rate had fallen to 85 or lower in less than two hours though a few required very much longer than this; in a detailed study of 15 consecutive patients whose apical rates were counted every five minutes, all having rates in excess of 120 before the drug was injected, slowing of the pulse to 85 or less occurred in two to ninety minutes with a mean time of thirty minutes.

Digilanid Intravenously.—Rimmerman (1945) used this agent intravenously in 9 instances in which emergency treatment was indicated; 4 cc. seemed to be the most effective dose usually but in 2 cases it was necessary to give as much as 8 cc. About three hours seemed to be required to exert an effect on the pulse and other symptoms; whenever possible, oral administration of one tablet of digilanid three times daily was started as soon as the intravenous dose had been given.

Digitaline Nativelle by Mouth.—Gold *et al.* (1942) found that the absorption of this preparation from the gastro-intestinal tract is almost complete, the oral and intravenous full digitalizing doses being for practical purposes identical. They therefore studied the rapidly digitalizing potentialities of a single dose of 1.25 mg. by mouth in 213 patients, some of whom had auricular fibrillation and others regular sinus rhythm, some ambulant and others confined to bed. Full digitalis effects were achieved in six to ten hours and sometimes within four hours. Since nausea or vomiting occurred in these patients only one-tenth as often as with an equivalent dose of digitalis, they felt that this single oral dose of digitaline nativelle was a satisfactory method of inducing rapid digitalization. In a subsequent report, Gold *et al.* (1944) reported that an initial dose of 1.2 mg. was fully as satisfactory as the 1.25 mg. originally used and that 0.2 mg. daily seemed to be satisfactory as maintenance dosage.

Maintenance Digitalis Dosage.—Gold (1942) stated that while the average daily maintenance dose varies a great deal, in most individuals it is about 3 grains (0.2 Gm.) of the leaf. However, the fact that decreasing need paces circulatory improvement indicates the necessity to be alert for opportunities to reduce maintenance dosage. The study of Weinstein *et al.* (1940) indicated that the tendency to prevent ventricular acceleration during exertion and emotional stress is one of the most valuable results of digitalis administration in maintenance dosage.

Digitalis Contraindications.—Gold (1942) made the statement that there are no contraindications to the use of digitalis. He was questioned by a number of competent men at the time, particularly regarding the presence of ventricular paroxysmal tachycardia, but he stood his ground that there are no contraindications to the use of digitalis.

Digitalis Combined with Other Drugs.—It has been shown to be dangerous to use the following drugs when digitalis is being taken: epinephrine, atropine (McFarland and Masson, 1927, animal studies only); ephedrine (Seevers and Meek, 1935, animal studies; Johnson and Gilbert, 1931, clinical); calcium (Gold and Edwards, 1927 and 1937; Lieberman, 1933; Golden and Brams, 1938; and others—animal studies, with which Smith *et al.*, 1939, disagreed;

Bower and Mengle, 1936, clinical). Quinidine also may be dangerous under some circumstances (see "Quinidine").

Clinical Toxicology of Digitalis.—By full digitalization is meant the administration of digitalis until its full therapeutic effects are obtained, at which time there usually also appear mild symptoms of toxicity. The physician should familiarize himself with *all* the signs of toxic action and not be content to recognize merely the most familiar ones, such as vomiting, drowsiness and excessive slowing of rate. The following is the list, arranged for convenience in memorizing:

Gastro-intestinal:	Nausea, loss of appetite, vomiting, diarrhea.
Circulatory:	Coupled rhythm, partial or complete heart block, simulation of any of the other spontaneous arrhythmias, diminution in secretion of urine, cold extremities.
Nervous:	Headache, drowsiness, mental confusion, visual disturbances.
Allergic:	Urticarial or scarlatiniform rashes, asthma, angioneurotic edema, etc. (all of these reactions are extremely rare).

To single out certain of these symptoms as invariably marking complete digitalization is erroneous and dangerously misleading. Gastric symptoms do not occur in all cases even if the patient is seriously poisoned, and an initial stimulation of the vomiting reflex may be succeeded by depression of the same, so that to rely greatly upon nausea and vomiting as measures of the degree of cardiac poisoning may be a very dangerous policy. Nor is the typical slowing of the heart always seen. To consider disturbances of vision as among the invariable signs of full digitalization is also misleading, for flickering disturbances are perhaps more often absent than present when digitalization is reached.

Against a background of animal experimentation of other workers, Massey *et al.* (1944) studied the effect of digitalis on the blood coagulation time in man, 24 patients being employed, some with and some without heart involvement; in each of these patients the coagulability of the blood was found to be accelerated during the period of digitalization. De Takats *et al.* (1944) also found that digitalis affects the clotting mechanism in man, but they employed a method of determining capillary coagulation time the accuracy of which had not so far as I am aware been determined by any other group than their own at the time of their publication. However, they felt no doubt that their studies indicated that digitalis favored the tendency to thrombosis, which would of course be especially significant in patients in whom other factors such as stasis or infection are already operating. In one of their cases doses of dicoumarol which ordinarily produced satisfactory levels of prothrombin were unable to do so during the administration of digitalis or urginin. A bit of time will have to pass and we shall have to have more studies before the true significance of these very interesting findings will be known.

Excretion of digitalis in the milk has not been demonstrated and almost certainly does not occur; there is therefore probably no danger to the infant if the nursing mother is digitalized, but even so I should think that a bit of extra watchfulness would not be amiss.

Squill Derivatives.—Squill is much older in the therapy of heart failure than is digitalis but has been justly overshadowed by the latter drug. Recently, there is some stir of interest in certain glycosides obtained from the crude drug, but I fail to see the advantage of cluttering up treatment with these new substances, since they have a toxicity practically identical to that of digitalis

and a therapeutic action in no wise superior so far as has yet been shown. The reader may find the papers of Carr and Mayer (1935), and Maher and Sittler (1936), of interest. The Council (1944) has accepted the following: (*a*) Scillaren, available in tablets of 1/80 grain (0.8 mg.), and a solution with the same amount per cubic centimeter. Dosage is said to be 1/40 grain (1.6 mg.) orally three or four times daily until compensation is established or minor toxic symptoms appear; dosage for maintenance of compensation, 1/80 grain two to four times daily. (*b*) Urginin, available in tablets of 1/60 grain (1.0 mg.). Dosage is said to be 3 mg. daily in divided doses at six-hour intervals until effect is observed; maintenance dose, 0.5 mg. to 1.0 mg. daily. (*c*) Scillaren-B is designed for intravenous administration; available in ampules each cubic centimeter of which contains the dose, 1/120 grain (0.5 mg.), which is not to be repeated within twenty-four hours.

Venesection.—Since venous pressure is recognized as being elevated in congestive heart failure, periodic waves of enthusiasm pass through the profession for the withdrawal of 400 cc. or more of blood. So-called "bloodless" venesection is also practiced—constricting the four limbs close to the trunk tightly enough to prevent venous return, the hope being to relieve the heart of a portion of its load without actual loss of blood. Few exact studies of the value of either of these measures are available, but Brams and Golden (1935) gave up the "bloodless" method after convincing themselves of its worthlessness, and having followed many patients after actual venesection they became skeptical of its value also. "It is possible that our patients had very little cardiac reserve, but we are inclined to rely on digitalis, sedatives and diuretics and to advise venesection only occasionally in right-sided cardiac failure." Levine (1940) stated that although venesection is not often indicated it will sometimes produce prompt relief in cases of marked engorgement of the liver, acute pulmonary edema, or paroxysmal dyspnea. Eggleston (1943) stated that the withdrawal of 500 cc. of blood from a patient in a pulmonary crisis of left ventricular failure (see below) does no harm and often is productive of dramatic relief. He also spoke well of applying blood pressure cuffs as tourniquets, inflating to just above the diastolic pressure, and releasing them progressively one after another around the circuit of the four extremities.

Oxygen.—Used as in pneumonia, oxygen therapy seems to have passed the peak of its popularity. The difficulties in arriving at a true judgment of the worth of the measure are very great. Katz *et al.* (1932), after a study of the literature and their own cases, felt that oxygen's role would probably prove to be to add to the comfort of patients who have definite pulmonary complications—congestion, consolidation, infarction, edema, and the like. "Miracles are not to be expected, and in the presence of prolonged, advanced, progressive cardiac disease, as is true also of other available therapeutic measures, oxygen cannot achieve the impossible." Eggleston (1943) would apparently like to use oxygen in every case of crisis in left ventricular failure (see p. 708).

Diuresis.—Usually rest and digitalis will in themselves result in considerable diuresis, but where edema is marked, as it is most likely to be in failure occurring in individuals with chronic nonvalvular disease with or without hypertension and arrhythmia, more direct diuretic measures are often productive of excellent responses. Indeed, the diuretic drugs not only promote fluid loss but in many instances also effectively relieve dyspnea. The studies of Friedman *et al.* (1935) showed that under favorable circumstances not only may the load on the heart be decreased but there may also occur an increase

in the organ's ability to carry its load; then too there are some studies indicating that a heavily digitalized patient may redigitalize himself after copious diuresis has concentrated digitalis in the body, but Gold (1942) said that "the evidence leaves something to be desired." With good average response the patient perhaps voids about 2000 cc. of urine daily, but in exceptional instances the amount rises to as high as 8000 cc. Fluid in the abdominal cavity and subcutaneous tissues seems to be equally well moved by the diuretics; that in the pleural cavity much less so. Lack of distensibility of the thoracic cage makes the latter much more disturbing to the patient also. I am sure that many agree with Christian (1936) in his advocacy of removal of this fluid by thoracocentesis as soon as any considerable dulness is detected on chest percussion. Volini and Levitt (1940) found that cerebrospinal fluid pressure is reduced by the effective employment of diuretic drugs. Levine (1940) found that in some instances effective diuresis is obtained only after abdominal paracentesis has released pressure on the renal vessels. In a few instances of resistant dependent edema, Southey tubes may be of value (see in Nephritis).

Mercurials.—These are the most effective diuretics so far developed but experience has shown that they act better when the body reaction is tipped toward the acid side, for which purpose various salts have been utilized, of which the three following are the most effective: ammonium chloride, ammonium nitrate and potassium nitrate; Keith, who introduced this preliminary acidifying therapy, preferred the potassium salt. The consensus is that any one of these salts must be given in amounts of 90 to 150 grains (6–10 Gm.) distributed throughout the twenty-four hours. They alone will often induce diuresis but not nearly so reliably or satisfactorily as when followed by a mercurial. Since the degree of induced relative acidosis is greater on the second and third days than subsequently, a satisfactory method is to give the salt only for two days before and on the day the mercurial is given and then to repeat this program when next diuresis is desired. These salts are very irritating to the gastric mucosa; Hayman (1936) pointed out that if they cause much vomiting the resultant swing toward alkalosis will defeat the purpose for which they were given. The following are probably satisfactory prescriptions, containing 15 grain (1 Gm.) of the drug per teaspoonful:

℞	Ammonium chloride	ʒj	30.0
	Anise water	ʒj	30.0
	Syrup glycyrrhiza to make	℥iv	120.0
	Label: 1 or more teaspoonfuls well diluted as directed.		

℞	Potassium nitrate	ʒj	30.0
	Syrup glycyrrhiza to make	℥iv	120.0
	Label: 1 or more teaspoonfuls well diluted as directed.		

Instead of these salts, Weigand (1935) and a few others have used 10 cc. of 20 per cent sodium dehydrocholate (decholin) solution, given intravenously at the time of giving the mercurial.

The mercurials most employed today are mersalyl (salyrgan)-theophylline, being as the name implies the mercurial agent mixed with theophylline, and mercupurin (mercurophylline), a mercury compound having theophylline incorporated in it. Formerly the mercurials were only given intravenously because the intramuscular injections were very painful, but now that they have the xanthine mixed with them they may be given intramuscularly with only very slight pain being caused. They are usually given in a single dose to

be repeated in a few days or weeks as needed; apparently effectiveness is not lost no matter how often medication is repeated, but Modell (1942) warned that the organic mercurials are excreted almost quantitatively in the urine only so long as there is good diuresis and that as diuresis falls off special caution must be taken when using these drugs since mercury retention may occur in the body. Adult dosage is 1 to 2 cc. of the ampule solutions, best practice probably being to administer the dose early in the morning in order to have the most vigorous diuresis over with before sleeping time at night. Evans and Paxon (1941) felt that for the patient confined to bed, injection every third day is probably the most satisfactory routine. Modell's (1944) study convinced him that the giving of two 1 cc. injections instead of one 2 cc. injection a week is distinctly advantageous since the patient is in greater comfort and less danger and actually experiences a 20 per cent greater total diuresis. The study of Ruskin and Herrmann (1944) indicated to them that an addition of about five times as much theophylline to the mixture would be advantageous, but preparations containing this much theophylline in addition to the mercurial are not as yet commercially available. Shaffer (1944) found that in 20 patients the addition of 500 mg. of ascorbic acid to the mercupurin injection effected a considerable increase in the resultant diuresis; it will of course require a large control study to substantiate this interesting finding. Mercurin, a mersalyl-theophylline preparation containing the mixture in suppository form, was found by Brightman and Batterman (1940) to be only about 60 per cent dependable and occasionally causing local discomfort and burning. Batterman and his associates have for several years been studying mercupurin administered orally; in their report in 1944 they stated that in a group of 42 patients mercupurin tablets had been found to be an effective and safe diuretic agent. For hospitalized patients they advocated a single dose of 5 tablets if moderately rapid diuresis is required; where gradual removal of the edema seemed more desirable, they found a multiple dose method of 2 tablets three times daily for two or three days quite satisfactory. An acid salt, used as in the case of parenteral injections, was found to enhance the diuretic action when mercupurin was given orally.

Of course these mercurial diuretic agents can give rise to a type of poisoning which is characteristic of mercury itself, *i.e.*, toxic action on the gastrointestinal tract and the kidneys, but these reactions occur very rarely. What has caused the profession more concern is the fact that these drugs like any other potent agents occasionally give rise to idiosyncratic reactions in susceptible individuals. Sometimes these reactions seem to be related to the particular compound used because another preparation can subsequently be employed with safety, but more often it would seem that they have been direct reactions to the mercury itself. Some of these reactions have been of a cutaneous nature, in others there have been chills or fever, or in others a state of shock, collapse, and urinary suppression, and there have been some deaths. But the number of deaths or even of severe reactions has been far below that which would indicate that these diuretic agents are not safe for routine employment. De Graff and Nadler (1942), reviewing the entire subject, stated that at Bellevue Hospital approximately 6000 injections, most of them intravenous, of mercurial diuretics are given every year, and that since 1934 they had known of no serious toxic reaction or death which might have been attributed to these drugs. Friedenson (1944) reported the case of a young woman who died of far advanced rheumatic heart disease, after having received over a period of twelve

years 627 injections of a mercurial diuretic with good diuretic response always, no reaction and no evidence of renal damage. These findings were the same in the case of Wood and Livezey (1942) whose patient had been given 350 injections.

Xanthines.—These agents are very little employed as diuretics nowadays because they are much less uniformly effective than the mercurials and they frequently cause nausea and sometimes vomiting; Gold (1942) and Wheeler (1942) were in agreement that at least nausea is caused in about 50 per cent of patients. The following are probably average dosages to be administered three times daily: theobromine sodium acetate (agurin), 7½ to 15 grains (0.5 to 1 Gm.); theobromine calcium salicylate (theocalcin), 7½ to 15 grains (0.5 to 1 Gm.); theophylline sodium acetate (theocin soluble) 3 to 6 grains (0.2 to 0.4 Gm.). The foregoing are all given by mouth, but the following may be given in several ways: theophylline ethylenediamine (aminophylline), 1½ to 3 grains (0.1 to 0.2 Gm.) three times daily by mouth, but this is high dosage; suppositories containing about 6 grains (0.36 Gm.) are available, or the drug may be given as a retention enema in the amount of 0.3 to 0.4 Gm. dissolved in water; and ampules containing 4 to 8 grains (0.24 to 0.48 Gm.) are available for either intramuscular or intravenous administration, the latter to be performed very slowly.

Urea.—Urea seems often to succeed as a diuretic where the xanthines fail; it is inexpensive and practically nontoxic so if there is an associated nephritis it is well to check the blood urea nitrogen now and then to be sure that excessive retention is not taking place. But the drug is extremely disagreeable in taste and many people simply cannot take it for that reason. Usual dosage is about 30 cc. of a 50 per cent solution of the urea stirred up in water or fruit juice three times a day; Wheeler (1942) said that many people find grape juice a particularly effective vehicle. Or the agent may be prescribed in the following form, in which one teaspoonful will contain 15 grains (1 Gm.):

℞	Urea	℥j	30.0
	Acacia powder	ʒiij	12.0
	Syrup of cinnamon to make	℥iv	120.0
	Label: 1 or more teaspoonfuls well diluted as directed.		

Catharsis.—Cathartics are not much used in these days of proper digitalis and diuretic therapy, but occasionally they still help to "wring out" the liver. For a list of saline cathartics, see Index.

Quinidine.—The principal matters pertaining to this drug are discussed in connection with auricular fibrillation unassociated with congestive failure. By common consent nowadays the routine use of the drug is not necessary in advanced organic heart disease with fibrillation, since the pulse can usually be reasonably well slowed even though not regulated by digitalis. Indeed, Brill (1937) pointed out that abolishing the arrhythmia may be undesirable, for some of these hearts seem to derive an advantage from the auricular fibrillation, and the temporary regulation of the rate with quinidine may offer no benefit commensurate with the degree of risk involved in the use of the drug. However, in certain otherwise hopeless cases where all other means of therapy have failed, the drug may occasionally be quite helpful. And there is also another class of patient, as referred to by Kohn and Levine (1935) and seen occasionally in most practices, that is sometimes remarkably helped by quinidine—individuals whose chief complaint is severe palpitation which

remains intractable even after thorough and maintained digitalization. Questioned about the combined use of quinidine and digitalis in the treatment of auricular fibrillation, Gold (1942) stated that occasionally if quinidine is given in very large doses after very large doses of digitalis there may occur a suppression of ventricular activity which can prove disastrous; however, he looked upon this possibility as merely an indication for the use of smaller doses and greater precaution.

Treatment of Pulmonary Crisis in Left Ventricular Failure.—These people with acute paroxysmal dyspnea and perhaps the beginning of acute pulmonary edema are seriously ill and in very great mental distress and it is imperatively necessary to relieve them quickly. In a Cornell Therapeutic Conference, in 1943, Eggleston discussed the matter very thoroughly. The essentials of the therapy advocated by him may be stated as follows: (*a*) The patient is placed in a sitting position in bed with the legs lowered if that is possible, which is of course not usually the case in the home; indeed one can often do little more than raise the head. (*b*) Morphine sulfate is then given in a minimal dose of $\frac{1}{4}$ grain (15 mg.) to effect relief of psychic distress; Eggleston did not favor the concomitant use of atropine unless in quite larger doses than those usually employed, and stated that he used it very little. (*c*) As soon as possible after giving a hypodermic injection of morphine the intravenous injection of aminophylline should be begun; Eggleston advocated the administration of $7\frac{1}{2}$ grains (0.5 Gm.) over a period of ten to fifteen or twenty minutes, using for this purpose a large syringe with a capacity of at least 20 cc. and a fine hypodermic needle which will serve as automatic mechanical control upon the rate of injection. Many men testify to the prompt relief from respiratory distress which is afforded by aminophylline in these cases. (*d*) Then Eggleston would bleed the patient, withdrawing at least 500 cc.; if this is not feasible he resorts to the so-called bloodless phlebotomy method with the application of tourniquets previously discussed under Venesection. (*e*) Oxygen is administered to the patient if and as soon as feasible. At the same Conference, Wolf (1943) presented the advantages of positive pressure oxygen therapy as developed largely by Barach. It is felt that during an attack of pulmonary edema intrathoracic and intrapulmonary pressure becomes lower as the result of obstruction to inspiration opposed to increased inspiratory effort on the part of the patient; positive pressure therapy would tend to relieve the negative pressure and thus reduce the return flow of blood to the congested lungs and the failing left ventricle. Oxygen under pressure also increases the oxygenation of the capillaries and thus opposes an increase in capillary permeability and the withdrawal of blood from the pulmonary capillaries into the alveolae in the state of negative intrapulmonary pressure obtaining in these patients. A further advantage of the pressure therapy is that by raising the intra-alveolar pressure, it tends to inhibit the formation and facilitate the absorption of the transudate.

Of course these patients are to be placed upon digitalis and the mercurial diuretics, the latter being of particular value, as pointed out by Modell (1943), since by the elimination of depots of fluid in the body which are not clinically apparent they tend to prevent redistribution of the water at night and to prevent the development of paroxysmal nocturnal dyspnea; as a matter of fact they are of prophylactic value for this purpose even when no apparent diuretic results may be experienced. Gold (1943) said that in his opinion active and persistent dehydration with diuretics is more important than almost any

factor he knows of in maintaining the patient with left ventricular failure in the best possible state.

Treatment of the Post-Failure Period.—Every effort should be made to build up the child's general health, and especially his exercise tolerance, through supervised play, and the like. Such things are not easily accomplished under supervision of the parents and therefore whenever possible the child should be sent to a convalescent home or a cardiac camp. For the adult, graded exercises, hydrotherapy and massage are held by the majority of physicians to be of considerable importance if the cardiac reserve is to be maintained or built up, though there are dissentient voices. For all who can afford it a long sojourn at a spa is ideal.

ANGINA PECTORIS

The attack of angina pectoris reflects a transitory period of undernourishment of a portion of the myocardium and is therefore really only a symptom of serious underlying cardiac disturbance rather than a disease *sui generis*. As is the case also in coronary occlusion, of which angina is usually only a premonitory sign (76 per cent of the 445 patients in the series of White *et al.*, 1943, died from cardiac causes), more men experience these attacks than women. The first seizure is usually had in the late fifties, fewer occur in the forties, and they are rare under thirty. There is no longer convincing evidence that the intellectual are any more frequently stricken than the working classes, but Amadeo's (1944) observation that the poverty-stricken, malnourished, chronically hookworm infected and hence severely anemic peasantry of Puerto Rico seldom exhibit the symptoms of angina pectoris is to me very interesting; his postulation that in these anemic individuals a vast net of collateral anastomotic coronary vessels has been formed would certainly seem worthy of exhaustive investigation. The history of the seizure as described by the patient is usually very typical, and it is upon it that diagnosis must be based for there are no constant and reliable physical signs or laboratory findings. The anginal attack is a sudden viselike gripping of the thorax, usually centered behind the sternum, with pain of variable degree but more often crushing than knifelike and accompanied frequently by a sense of impending death. When the pain radiates it is nearly always into the left shoulder and down the left arm, but sometimes it extends up into the jaws also. Such an attack may be precipitated by unusual exercise or, in the more severe cases, by the most ordinary movements of the body; in some cases exposure to cold or emotional stresses or crises are the more potent causes; and there are some individuals who experience most of their attacks at night in bed. The paroxysm in its more severe form is characterized also by one other conspicuous feature, the immobility of the patient; he may elect to stand or to sit bolt upright (he rarely reclines), but whatever his posture he retains it fixedly, rarely even emitting a groan despite his pain, until the attack has passed. The paroxysm may last only a few seconds or it may persist for several minutes; if it lasts more than one-quarter hour, the observer does well to suspect coronary occlusion.

The most extensive prognostic study in angina pectoris of which I am aware is that of White *et al.* (1943), 445 of whose 497 patients had an average duration to death of 7.9 years while the average duration in the 52 still alive was 18.4

years. Since the average duration to date of publication for the combined dead and living was 9.0 years, which it was reckoned would ultimately increase when all the survivors succumbed to a figure approximating 10 years, the conclusion may reasonably be drawn that the expectation of life after the first anginal attack is about twice the period of five years which has heretofore been widely regarded as the true figure.

The first complete description of angina pectoris was that of Heberden before the Royal College of Physicians in London, in 1768.

IMMEDIATE RELIEF OF PAIN

Nitrites.—Amyl nitrite by inhalation often brings relief in thirty seconds to one minute; it may be conveniently carried on the person in the form of a box of the "pearls," one of which is crushed in the handkerchief for inhalation. But the odor is often objectionable to the patient and others who may be nearby when the necessity to use the drug arises; relief is also not so certain as with nitroglycerin. This latter drug may be prescribed in 1/100 grain (0.6 mg.) hypodermic tablets; they are not volatile, do not deteriorate quickly and are less expensive than amyl nitrite. The dose is 1 tablet, more or less, dissolved under the tongue, not swallowed; the full effect is more slowly achieved than with amyl nitrite—two to three minutes usually. While many patients have taken quite large doses of nitroglycerin with apparent impunity, a small number of pronounced reactions has been recorded: precipitate drop in blood pressure, severe headache and palpitation, and considerable discomfort for forty-eight hours. Sprague and White (1933) observed such reactions only three times in their 900 patients, but they pointed out that it is an easy routine in the office to try 1/400 to 1/200 grain (0.15–0.3 mg.) sublingually in each new case. Master said, in 1935, that he believed these small doses to be routinely as effective as the larger ones. Christian advised many years ago that the patient be urged to remove the undissolved portion of the tablet as soon as relief is experienced.

Alcohol.—A stout drink of whiskey or brandy, or any hard liquor taken "neat" with very little water to "chase" it, may bring quick relief in the anginal attack; this measure is said to be effective occasionally when the nitrites fail.

SUBSEQUENT THERAPY

Angina pectoris is a symptom which will usually be relieved by the measures above described. But it is also a symptom pointing toward the existence of a potentiality for dysfunction of the myocardium, the attacks being initiated by so-called trigger mechanisms which vary with individuals. In one individual it will be excessive physical strain, in another excessively prolonged mental application, in another emotional stress, in another over-eating, etc. Obviously, therefore, some attempt must be made to effect such alterations in the mode of life of the anginal patient as will assure lessened frequency of attacks. Then too one must employ whatever drug or other measures experience has shown possess some likelihood of spacing the attacks further apart or damping them down when they occur. Now the individual who has had an attack of coronary occlusion may also subsequently have anginal attacks, and since the measures employed in him are the same as those employed in an individual who has experienced angina pectoris but has not yet had an attack of occlusion, I am describing these measures all together here, leaving it to the reader's judgment

to determine in given instances which measure is more particularly suited for his patient who has recovered from an attack of coronary occlusion or is still only in the stage of experiencing attacks of angina pectoris antecedent to occlusion. In addition some measures are described for the combating of excessively severe or persistent pain whether in occlusion or in angina pectoris.

Mode of Life.—If the overworked, overworried, overwrought individual with coronary disease can be brought to relinquish in whole or in large part his professional or business affairs; and can be brought to adopt the mode of life of a person of indolent habit and independent means, and to model his temperament upon that of the cow; and can be induced to journey south in a leisurely fashion during the inclement months, going preferably to a spa; and can be reeducated to eat slowly of light foods in small amounts—that is to say, if all that is practically impossible for the average competing individual in a work-a-day world can be accomplished—then the patient may be said to have the best chance of prolonging his life. I do not know of any well-substantiated evidence that altitudes of 10,000 or 12,000 feet, which is about the average ceiling of transport planes in this country, are harmful, though it is commonly said that these individuals should avoid such altitudes. Many physicians do not permit sexual intercourse; it seems to me that in a certain sort of individual the loss of this right might in itself provoke an attack.

Diet.—Full heavy meals and especially gas-forming foods are to be avoided. Articles of food not well borne must be discovered by the individual patient; indeed, having reached the age of most of these patients he has long known the things which disagree with him and needs only to eliminate these from his diet. Levy (1937) showed that coffee will induce cardiac pain in some individuals. Hydrochloric acid with meals is helpful to some patients; carminatives after meals are not contraindicated (see Index for prescription).

There are indications that obesity is a handicap. More than half Goldsmith and Willius' (1937) series of 300 patients at the Mayo Clinic were overweight; in the series of 80 fatal cases of coronary disease in soldiers in the American Army, reported by French and Dock (1944), the most striking presumable predisposing factor was overweight, which was present in 91 per cent of the cases. However, in reducing the weight of the victim of coronary disease, thyroid extract should definitely not be used.

Tobacco and Alcohol.—It seems to me that there has been considerable misunderstanding of the report of White and Sharber (1934), who compared the past alcohol and tobacco habits of 750 angina pectoris patients with 750 individuals who did not have angina. They found no evidence that the use of either of these drugs of addiction played an important role in the genesis of the malady, but they also stated that in occasional cases the use of tobacco apparently aggravated or precipitated attacks and indulgence in alcohol helped to prevent or to relieve them. Many doctors are overlooking the latter part of this evidence in their joy at finding that they can continue to smoke without endangering their coronaries—perhaps it would have been better to use the word "surprise" instead of "joy" above, for most of us really suspected the habit to be dangerous. The evidence from Willius' section on cardiology at the Mayo Clinic, published by English *et al.* (1940), while not conclusive certainly pointed toward smoking as a possibly contributory factor, especially in the younger age groups. May I say that when or if I come down with coronary disease I shall stop smoking if I can and at once change my drink from beer, which distends the stomach, to hard liquor?

Nitrites.—The disagreeable effects of drugs of this group, occasionally seen when amyl nitrite or nitroglycerin is used for the relief of an attack of angina, are much more frequent accompaniments of the routine use of the longer-acting members, the tetranitrates and sodium nitrite. But in an individual who is having many anginal attacks during the twenty-four hours it is sometimes possible to lessen both their number and severity for a time at least by the use of these preparations; the result is said to be especially gratifying in those whose nocturnal attacks make the nights very miserable. Erythrityl tetranitrate tablets of the U.S.P. are available in $\frac{1}{4}$- and $\frac{1}{2}$- grain (0.015 and 0.03 Gm.) tablets; the dose is $\frac{1}{2}$ to 1 grain every four to six hours; mannitol hexanitrate may also be used in the same dosage. These salts are all rather expensive. Sodium nitrite is cheaper but very irritating to the stomach. Many practitioners who formerly used the latter drug thought it more effective when combined with sodium or potassium iodide. The sodium nitrite dose is 1 to 3 grains (0.06–0.2 Gm.) in tablets or capsules.

Xanthine Vasodilators.—Many physicians have thought these drugs helpful, though most patients are somewhat upset by them; the untoward effects are nausea and sometimes vomiting, a burning pain in the epigastrium or under the sternum, palpitation, dizziness, headache, "nervousness," and a few other minor complaints. The drugs of the group and their dosage are given in Heart Failure. Not only tolerance but also cross tolerance to these drugs seems to be acquired by an occasional patient; some men have the medication taken for four consecutive days of each week and omitted on three, and they alternate theobromine with a theophylline preparation. The studies of Levy *et al.* (1940) pointed strongly toward the ability of aminophylline to postpone the appearance of pain; McMahon and Nussbaum (1940) concluded that favorable changes in the electrocardiogram often result from the intravenous administration of this drug. LeRoy (1941) gave aminophylline or placebos to 68 patients over a period of two years; he said that the drug benefited about 75 per cent of the patients, placebos and sedative drugs about 20 per cent. However, there is a reverse to the coin, for in two carefully controlled studies, those of Evans and Hoyle (1933) in England, and Gold *et al.* (1937) in the United States, there was failure to adduce any proof that these drugs are actually of value in coronary disease. In the latter studies, 209 courses of treatment with xanthines in 100 patients were alternated with courses of placebos or some other agents; the patients could detect no differences. Boyer (1943), reviewing the matter for the Council on Pharmacy and Chemistry, found the evidence for the usefulness of the xanthines in the treatment of coronary disease "far from satisfactory"; but Gilbert (1944) still highly recommends them. So the matter remains controversial!

Papaverine.—In 1942, Elek and Katz reported the highly successful employment of papaverine hydrochloride in about three fourths of 17 intensively studied patients with the anginal syndrome. The originally recommended dosage was $1\frac{1}{2}$ grains (0.1 Gm.) three or four times a day, but many men are now using the drug in considerably higher dosage; according to N.N.R. (1944) single doses of even 15 grains (1.0 Gm.) are said to be nontoxic. I have heard a great deal of the satisfaction with which this drug is frequently employed, but have seen nothing in the literature since the original report.

Sedatives and Codeine.—Many of these patients profit at times from the judicious use of sedatives and hypnotics (see Insomnia). Sproull (1936) said that in the elderly, thin, arteriosclerotic individual, still actively bustling about

in life despite his enlarged heart and anginal symptoms, codeine sulfate is very valuable. He begins with $\frac{1}{8}$ grain (8 mg.) four times daily and after about ten days reduces the dose as much as possible. Riseman (1943) also reported that codeine was helpful in some of his patients.

Nicotinic Acid (Niacin).—Neuwahl (1942) reported the administration of 100 to 300 mg. of this agent by intravenous infusion in 6 cases, in most instances giving 6 infusions during a period of about three weeks. There was said to have been subjective and objective evidence of improvement in the patient's condition in all his cases and that it had been maintained during the six months preceding the report. This type of therapy has been much used since Neuwahl's report and it is hoped that someone is presently engaged in making a thorough study of it and that we shall soon have an authoritative report on a large number of cases. The drug is also being administered by mouth, which type of medication, indeed, Neuwahl reported satisfactory but transient in its effect.

Sex Hormones.—There have been a number of favorable reports of the use of sex hormones in the anginal syndrome since the first report of Edwards *et al.* in 1939. The most favorable report is perhaps that of Lesser (1943) who used testosterone propionate in 25 mg. doses for a total of 5 to 25 injections, with an average of 11 injections, the number of patients so treated being 41 men and 5 women. It was said that in each of these cases subjective improvement was reported and that in 4 of the patients exercise tolerance tests substantiated the report. No deleterious results were noted and the action of the agent seemed to continue for from two to twelve months after the cessation of its employment. However, Levine and Likoff (1943) carefully studied the use of this agent in 18 patients treated for four weeks and 1 patient for seven weeks, and they felt that, considering the spontaneous variation in the clinical course of angina pectoris, they were unable to conclude that testosterone had been beneficial in their cases. Unfortunately a sort of subclassification of angina cases has already begun to be made on the basis of response to this drug, for McGavack (1943), writing of 8 patients who responded to testosterone but not to vasodilator drugs, differentiated them as individuals having angina pectoris in association with the "male climacterium."

Iodides.—Riseman (1943) reported that 12 per cent of a group of patients who were unresponsive to most other measures were helped by potassium iodide in 15 grain (1.0 Gm.) enteric-coated tablets given three or four times daily.

Cobra Venom.—Parsonnet and Bernstein (1940) were pleased with the results of cobra venom therapy in 5 otherwise intractable cases: 5 mouse units intramuscularly repeated on the following two days; then tailing off every other day; finally twice a week. Riseman (1943) also found the agent of value in some cases. Cobra venom is very slow in producing its effects and is therefore not at all suited to the control of pain in the acute attack.

Surgical Measures.—*Cervical sympathectomy:* This operation has been practically abandoned, though I believe a few surgeons continue to perform it in patients under forty-five years of age; Raney (1939) described a "preganglionic" resection, but I have seen no reports of anyone else performing this operation. *Paravertebral alcohol block:* This procedure has fared somewhat better. Levy and Moore (1941) reported relief in 77.5 per cent of 40 patients, the relief being marked and permanent (8 cases followed more than six, and 2 cases more than nine, years) in 47.5 per cent. In 5 cases pleural effusion

developed on the left side but was absorbed without aspiration within a week. Most of the patients suffered from painful intercostal neuritis which lasted from a few weeks to several months. Hirschboeck and Gillespie (1942) reported a case of their own and cited two from the literature in which serious injury to the cord had resulted from paravertebral alcohol injection. Riseman (1943) said that alcohol injection rarely results in any increase in exercise tolerance. *Grafting operations:* Claude Beck (1937) attempted to increase the blood supply to the myocardium by grafting tissues upon the heart, an experimental procedure in hopeless cases which has at least the merit of supreme audacity; others, both in England and America, have reported satisfactory results from this operation. *Total thyroidectomy:* In the main there does not any longer seem to be much interest in this operation, though Riseman (1943), of Harvard, considered it the surgical procedure of choice in patients who were adequate surgical risks, had normal basal metabolic rates, prolonged but not progressive symptoms, and a fair life expectancy.

Physical Therapy.—Raab (1940) attempted to relieve the symptoms of angina pectoris by restricting the acute discharges of adrenalin through roentgen irradiation of the suprarenal glands; success was claimed in 76 of 100 cases. This is a new and radical type of treatment and of course the results will need independent confirmation before one can consider them valid; furthermore the control of such an experiment would be difficult in the extreme. The same objection applies to the use of short-wave diathermy, which has been much employed by European workers.

CORONARY INSUFFICIENCY AND OCCLUSION

The correlation of bedside and pathologic findings in coronary occlusion with the resultant recognition of it as a definite clinical syndrome, has taken place only in the twentieth century, in our own country largely as a result of the pioneer work of Herrick. The interested reader is referred to the fine studies of Blumgart *et al.* (1940) on the relationship of the clinical and pathological findings in coronary disease, which it does not seem within my province to review here save to say that in general it seems conclusive that death occurs whenever a sufficiently large area of the myocardium undergoes ischemia, with or without necrosis, or when, because of ischemia, asystole, ventricular fibrillation, or congestive failure occurs. Some students in this field, notably Master (1944), would confine the term "coronary occlusion" to those cases only in which there is definite thrombosis with myocardial infarction, preferring to apply the term "coronary insufficiency" to those cases in which the pathological lesion is a focal disseminated necrosis in the subendocardium and papillary muscles but without occlusion. They make the point that although the attack of acute coronary insufficiency simulates that of complete closure of a coronary vessel, the severity of the lesion is usually less and the signs and symptoms are usually much less pronounced than one sees in coronary occlusion. Master holds that sudden death following excitement or exertion is often the result of an acute coronary insufficiency but that such external factors as effort and excitement play no part in the precipitation of a complete coronary occlusion. The victims of coronary disease are usually past fifty years of age; at least half of the men and practically all of the smaller number of women,

are said to be hypertensive and the women also usually diabetic. However note should be taken of the 80 cases of fatal coronary disease in soldiers aged twenty to thirty-six reported by French and Dock (1944); the basis of the occlusion was found to be arteriosclerosis in all cases. There is increasing evidence that the incidence of attacks is greatest in winter. Except when death is sudden, the salient features of an acute coronary seizure are the following: (*a*) severe substernal or upper abdominal anginoid pain, sudden in onset but of long duration (though according to Steincrohn, 1940, there is a characteristic rhythmicity and periodicity of the pain during the attack); (*b*) pinched, ashen gray or very pale facies often associated with a feeling of impending death, but usually without the fixation in position so characteristic of angina pectoris; (*c*) cold sweat and cold extremities; (*d*) acute emphysematous distention of the lungs with dyspnea or orthopnea and moist crackling râles at the lung bases, together with the onset of acute heart failure; (*e*) an early thready pulse with almost any form of arrhythmia; (*f*) rapid and often prolonged reduction in systolic pressure; (*g*) a diffuse, scarcely palpable cardiac impulse; (*h*) distant heart sounds and often a gallop rhythm; (*i*) a localized, evanescent pericardial friction rub; (*j*) short, mild fever with leukocytosis and a rapid sedimentation rate; (*k*) changes in the electrocardiogram which, as Willius (1940) emphasized, only one with a thorough knowledge of the limitations as well as the advantages of this instrument can interpret. Coronary occlusion is often associated with or is the cause of abdominal signs and symptoms, and occasionally it will closely simulate an acute surgical condition of the abdomen. Also in instances in which there are not such typical cataclysmic attacks, the coronary origin of the symptoms may be easily overlooked in preoccupation with the patient's "indigestion"; but the history of prior events will often give an inkling of what is happening. Master *et al.* (1941) found that in nearly half of their 260 patients premonitory symptoms had been experienced; fatigue, weakness, gastric distress, dyspnea, palpitation, nervousness, dizziness, angina. Occasionally occlusion may occur without any type of pain at all.

The study of Master *et al.* (1942) of 202 patients, both private and clinic and of all classes and types of occupation, clearly indicated that an attack of acute coronary occlusion in itself need not be looked upon today, as it was a few years ago, as invariably constituting sufficient reason for permanent disability. Recovery from the acute attack was found to be good or complete in over one third of their patients, *i.e.*, they had no symptoms of diminished cardiac reserve on routine activity. One half were able to return to work, usually full time, and cardiac reserve as measured by function tests was normal or only slightly abnormal. Drake (1940) reported the record in longevity, I believe, a man who returned to his usual occupation after suffering a myocardial infarction at the age of forty; at sixty-seven he developed angina; at seventy-five another attack of coronary thrombosis which did not seem to change his physical condition after healing had taken place; at seventy-eight a third coronary thrombotic attack from which he recovered after many weeks; and sudden death in a nocturnal attack of angina at the age of eighty.

THERAPY

Nursing Care.—When he is first seen the patient is usually in a state of nervous if not actual circulatory shock, and therefore it is best if at all feasible to put him to bed at once wherever the attack has caught him, perhaps even

without removal of clothes, for it is of the utmost importance to obtain quickly the maximum physical and emotional quiet with the minimum expenditure of either emotional or physical energy. The obtaining of competent nursing assistance and the relief of the suffering are affairs of first moment, removal to the hospital or to his own home of secondary importance. Then the siege must begin, a campaign whose sole object is to keep the patient *lying down* in bed for six or preferably eight weeks, to keep him quiet and unagitated during that time, and to cajole and induce him to like it. In the beginning he must not be permitted to move even enough to feed himself, and should be allowed to see as few people and attend to as few affairs as possible. The use of sedative drugs is not contraindicated (see Insomnia). Two or three months of enforced invalidism is an ordeal which few persons will accept without at least some show of stubborn resistance; but if the patient does not know with certainty that such a period lies before him there will likely be much less struggle. Riesman admirably said "The tactful physician will achieve his end by giving an answer which is true but not necessarily specific." Gradual propping in bed may begin a little before the sixth to eighth week, depending upon the severity of the attack, then in a few days more the feet may be allowed to hang over the side, and finally the patient may be got out by very slow stages so that he is walking about by the eighth to tenth week (the scar is thought to be firm now), perhaps slowly climbing stairs, if he must, in another month. I am merely condensing here the experience of many men in average cases; no time rules for these stages can be set, of course. The signposts that too much is being attempted: sensation of choking, return of pain or pressure, cyanosis, shortness of breath on exertion; this patient must be returned to bed.

The above-described orthodox type of treatment of these cases by prolonged bed rest is predicated upon the following hypothetical advantages: (*a*) liability to cardiac rupture is lessened; (*b*) cerebral anoxia as a result of the circulatory collapse is lessened; (*c*) such prolonged rest leads to the formation of a firmer and smaller scar. Recently, however, Harrison (1944) has shocked and surprised us into a reconsideration of the justification for a prolonged period of rest. He says that since most instances of rupture occur within the first two weeks, the advantage of complete rest beyond this period is not apparent for the purpose of avoiding such ruptures; likewise he says that since in most patients circulatory relapse of serious degree has disappeared within the first week or two, the theoretical advantage of maintaining the patient in the recumbent posture in order to counteract cerebral anoxia disappears after that time. Furthermore he questions whether a firmer and smaller scar is produced in a recumbent position since in his opinion cardiac work per beat is probably no greater and may be somewhat less in the sitting position than in the recumbent posture because the decline in blood pressure in the latter position is usually at least counterbalanced by the increased stroke volume in this posture. Theoretical disadvantages of prolonged rest in bed for these patients are listed by Harrison as follows: (*a*) recumbency invites edema of the lungs given a tendency toward the development of congestive heart failure; (*b*) both pulmonary infarction and a second myocardial infarction may be the result of rigid restriction of activity with consequent reduction in blood flow; (*c*) hypostatic pneumonia is especially apt to occur in elderly patients who remain in bed over a long period of time; (*d*) years of psychic invalidism may be brought about as a result of insistence on excessive caution during a period of many months. Tentatively, Harrison offered the following

plan of treatment, to be modified of course according to the status of the individual patient: (1) allow the patient with congestive heart failure out of bed several hours a day as soon as severe dyspnea at rest has subsided; (2) do not prescribe recumbency following myocardial infarction for a longer period than two to three weeks after the more acute and alarming symptoms have subsided, do not enforce recumbency on patients who are more comfortable sitting, and get elderly patients out of bed sooner than younger ones; (3) do not consider rest in bed for more than a day or two indicated in the treatment of angina pectoris except in patients in whom increasingly frequent and prolonged attacks at rest indicate the likelihood of impending myocardial infarction; (4) keep the activity of all patients with severe forms of heart disease below the symptomatic threshold, *i.e.*, less than that amount which induces dyspnea or pain. It is going to be extremely interesting to see what effect this new therapeutic concept will have upon the treatment of cardiac breakdown in the years to come.

Emergency Measures.—*Opiates.*—It is practically always necessary to give morphine, $\frac{1}{4}$ to $\frac{1}{2}$ grain (15 to 30 mg.), or dilaudid, 1/48 to 1/24 grain (1.25 to 2.5 mg.), at once. Larger doses are required to control this than any other pain—perhaps one grain of morphine in the first twelve hours; sometimes it is necessary to give it by vein. However there are many careful clinicians who feel it is often best not to try to give enough morphine to conquer the pain *completely* in all cases. Scopolamine hydrobromide (hyoscine hydrobromide) may be safely used in addition to one of the opiate injections, in dose of 1/300 to 1/100 grain (0.2 to 0.6 mg.), but it is perhaps best not repeated under several hours. When pain persists for several days, attempt is usually made to change to codeine in doses of $\frac{1}{4}$ to $\frac{1}{2}$ grain (15 to 30 mg.) every four hours.

Other Analgesics.—In a morphine-resistant case, Hirsch (1936) successfully employed evipal solution, and I have heard of the newer pentothal being employed also; but I should think one would have to proceed extremely cautiously with these agents. In two morphine-resistant cases, Riesman stopped the pain at once by application of leeches to the precordium. Lilienthal (1943) also championed this method of treatment. Love (1937) found trichlorethylene inhalations helpful in a morphine-resistant case, but Willius and Dry (1937) were disappointed in their results.

Vasodilators.—It certainly seems to me that in the acute attack with circulatory collapse and a low blood pressure the use of agents of this group is at least theoretically extremely inadvisable; however, there are a few men who maintain that if these drugs are used with proper precaution they will effect great relief. Gilbert (1944) said he gives atropine sulfate, 1/100 to 1/75 grain (0.6 to 0.8 mg.), hypodermically routinely in all cases where the occlusion is at all recent, the theory being that reflex vasal constriction of the arteries in the uninvolved heart muscle is thus counteracted. Gilbert also felt that aminophylline solution, 10 to 20 cc., may be valuable if injected very slowly intravenously; also he advocated the intravenous injection of 1 grain (60 mg.) of papaverine hydrochloride, using a somewhat larger dose if the drug is given hypodermically. Falk (1942) also spoke well of the intravenous emergency employment of papaverine.

Stimulants.—To combat the peripheral circulatory failure, the most widely used drugs are metrazol, coramine and caffeine; I do not know that anyone has shown how much worth they really are.

Oxygen.—In recent years Barach and Levy have been advocating the use of

oxygen in cases of coronary thrombosis (for methods see Pneumonia). Many men testify to its ability to relieve dyspnea, cyanosis, restlessness and pain—Gilbert (1944) felt that it should be routinely employed in all cases. Boland (1940) made the important point that in his experience such concentrations as are ordinarily reached in a tent do not suffice for complete relief but that this end is achieved by the employment of one of the newer types of inhalation apparatus which will deliver the higher concentrations—80 to 100 per cent—which he felt are necessary.

Dextrose and Insulin.—It is customary with a number of men to give a slow infusion of dextrose-saline started as soon as seems feasible. Some years ago Smith (1933), in England, reported the use of insulin also, believing that it would promote the early resolution of atheromatous changes in the coronary arteries. I do not think this has come to anything however as most men seem unalterably opposed to the use of insulin in coronary disease.

Diet.—For the first two or three days the patient is very unlikely to desire much food. Sipping of cold charged water or swallowing small bits of ice will usually control nausea; the addition of bismuth subcarbonate and sodium bicarbonate, each in 15-grain (1 Gm.) doses, will almost certainly do so; unfortunately, however, the nausea and possibly vomiting induced by morphine are not easily controlled by any means that I know—the employment of benzedrine sulfate (amphetamine) for this purpose, successfully reported by Guyot (1941), seems to me a very radical procedure; indeed, I believe the consensus to be that benzedrine is contraindicated at least during the acute stages of coronary disease. Dry toast, chicken, buttermilk, apple sauce, strained vegetables, tea or coffee may all be added gradually and in small quantities. Throughout the bedridden period the food intake must be kept small; Master and his associates perhaps ritualize the thing more than most others and actually keep their diets lower, but they also describe good results. For at least three and preferably four weeks they limit fluids to 1000 or 1200 cc. and calories to 800; the following is a sample diet containing 100 Gm. carbohydrates, 50 Gm. proteins, 20 Gm. fat, with adequate vitamins and calcium. They claim as much reduction in basal metabolic rate with this regimen as is accomplished by thyroidectomy and that patients feel so well under it that persuasion is often required to get them to increase their food intake.

800 Calorie Diet (Master, Jaffe and Dack, 1936)

	Sample Menu
Breakfast	
100 Gm. 12 per cent fruit	½ medium orange
10 Gm. cereal	2 tablespoons cooked cereal
200 cc. skimmed milk	1 cup
1 egg	1 egg
15 Gm. bread	½ slice
Dinner	
60 Gm. meat	2 ounces meat
100 Gm. 3 per cent vegetable	½ cup spinach
100 Gm. 12 per cent fruit	3 plums
15 Gm. bread	½ slice
200 cc. skimmed milk	1 cup
Supper	
1 egg	1 egg
100 Gm. 3 per cent vegetable	¾ cup canned string beans
100 Gm. 12 per cent fruit	1 medium peach
15 Gm. bread	½ slice
200 cc. skimmed milk	1 cup

Care of the Bowels.—Urinal and bed pan will of course be used throughout the entire time. Straining had best be avoided by the use of liquid petrolatum. It is best to permit the costiveness induced by the opiates in the beginning to persist for several days, which can easily be done as the patient is taking practically no food; a larger dose of cathartic than is usual will then be required to obtain the first movement.

Digitalis and Quinidine.—I think that upon the whole the profession is fearful of the use of digitalis in coronary occlusion in the belief that it may: (*a*) rupture the infarct through increasing the force of the heart's contraction; (*b*) predispose the heart to ventricular tachycardia; (*c*) constrict the coronary vessels. But such an authority as Gold, who has gone into this matter extensively, is certain that there are no grounds for any of these fears. He feels that the indications for digitalis in coronary occlusion are precisely those that would obtain otherwise, *i.e.*, the drug should be used if there supervenes an auricular fibrillation or a right or left ventricular failure. Such disturbances occur very rarely during the early days of a coronary episode and not always by any means at a later period or during the subsequent attacks; therefore there can be no thought or excuse for routine digitalization of these patients. When the drug is indicated and employed, Gold would not have it used in a hectic fashion—allow a somewhat longer time than usual for the accomplishment of full effect. Willius (1944), while expressing himself essentially in agreement with the position of Gold, felt that unless the onset of the failure is precipitous and severe, abundant clinical experience seems to justify a resort to complete rest and the use of the mercurial diuretics before hastening to use digitalis.

Ventricular tachycardia being an arrhythmia much feared after coronary occlusion, there has arisen some interest, probably initiated by Levine (1936), in the "prophylactic" use of quinidine to prevent this occurrence; ventricular tachycardia going over into fibrillation of course means death. Borg (1939), employing quinidine sulfate 3 grains (0.2 Gm.) three times daily in a large group of clinic patients of the sort in whom sudden death was to be expected, felt that the drug probably lessened the incidence of such deaths. Woods and Barnes (1941), at the Mayo Clinic, seemed convinced that it is rational and probably important to give the drug to any patient who has had an occlusion, particularly if the patient is experiencing frequent premature ventricular contractions. However, it is my impression that Gold is still unconvinced that this "prophylactic" treatment has merit.

AORTITIS AND ANEURYSM

(See under the *Treatment of Cardiovascular Syphilis*)

THROMBOANGIITIS OBLITERANS

(*Buerger's Disease*)

This peculiar disease, first described by Buerger in 1908, is an inflammatory affection of the deep-seated arteries and veins and the superficial veins of the lower extremities, occasionally of the upper extremities. It occurs principally

in middle-aged males, though women, in whom it seems to be a milder affection, are also very occasionally afflicted. We nowadays do not look upon this as almost exclusively an affliction of Jews; of Horton's (1938) 927 cases, 670 were in Gentiles. The etiology of the disease is unknown, but it is generally conceded that excessive smoking plays some part; there are now available several studies showing that peripheral vascular constriction accompanies the act of smoking. The studies of Theis and Freeland (1941) suggested that disturbance in the utilization of oxygen consequent upon constriction of vessels is one of the conditions underlying the pathology of the disease. Sulzberger and Harkavy, whose findings were later confirmed by Green (1942), independently arrived at the belief that there may be an allergic hypersensitiveness to tobacco in many cases; Westcott and Wright, however, did not share this opinion at the time they last committed themselves in the literature. Kaunitz' interesting thesis, that Buerger's disease and related vasomotor and trophic disturbances are the present-day expression of ergotism, gained support from Klein's (1937) showing that our common cereals are frequently fungus infested. McGrath's (1935) animal studies suggested to him the possibility that the female rarely develops the disease because of the protective action of the estrogenic ovarian substance. Rabinowitz (1933) looked upon impaired phospholipin metabolism as responsible for all findings. Goodman (1941) very interestingly contended that thromboangiitis obliterans is a late manifestation of typhus fever, a position accepted by Ferro-Luzzi (1942) after his study of the disease in Italian Eritrea. Thompson (1944) believes that the disease may be caused by hypersensitization to one of the dermatophytes.

The character of the lesions suggests either a toxic or bacterial exciting factor; there is acute inflammation with occlusive thrombosis, organization or healing, canalization of the clot, disappearance of the inflammatory products, and the development of fibrotic tissue that binds together the artery, vein and nerves. The cardinal signs and symptoms of the disease, which usually develops insidiously, are severe constant pain in the calf and foot and also intermittent pain of the claudication type; pallor of the limb when it is raised above the horizontal position and great redness (rubor) when it is dependent; coldness of the extremity; and lack of pulsation in the arteries affected. Migrating phlebitis of the superficial veins is of frequent occurrence. Ultimately, ulceration and gangrene occur in the great majority of cases.

Cohen and Barron's (1936) review of the autopsy literature revealed thromboangiitis obliterans as probably a generalized disease process which may affect vessels anywhere in the body. Hausner and Allen's (1940) observations at the Mayo Clinic substantiated this viewpoint: 5.7 per cent of 500 patients had coronary involvement, 2 per cent cerebrovascular involvement, and there were three cases of abdominal and one of pulmonary involvement. In 1942, Davis and Perret reviewed the literature and added four interesting cases of their own of the purely cerebral form; Scheinker (1944) also very thoroughly described a cerebral case.

THERAPY

This disease being of unknown etiology, of serious import, and as yet without a specific remedy, it is to be expected that a large number of remedial agents and measures shall have been tried. I shall discuss here only those that seem to be holding their own as therapeutic procedures, but in attempting to evaluate them the reader should give full consideration to the following state-

ments of Perla (1925): "Thrombo-angiitis obliterans is an extremely chronic disease, often lasting as long as fifteen or twenty years. More than 80 per cent of all cases give a history of remissions during which the patient is free from all symptoms. These remissions occur spontaneously at almost any stage of the disease and last from a few months to several years, frequently as long as five, ten and even fifteen years. . . . Temporary arrests have been reported as cures following almost every new therapeutic innovation. In this disease, particularly, a temporary arrest of one year is not evidence of more than a remission." In Horton's (1938) review of 948 cases at the Mayo Clinic, it was revealed that approximately 30 per cent of patients require an amputation within three years of onset of the disease, 40 per cent within five years and 60 per cent within ten years.

Smoking.—All authoritative students of this disease are in agreement that tobacco must be absolutely interdicted; witness the following statements. Horton (1940): "We at the Clinic are of the firm conviction that all patients who have thromboangiitis obliterans should stop smoking." Allen (1939): "Hardly new, but well worth emphasizing again, is the importance of complete cessation of smoking." Wright (1940): "Good results are to be expected from the general treatment outlined here provided the patient will completely stop smoking."

Alcohol.—In contrast to tobacco alcohol is definitely a dilator of the peripheral vessels. All observers use it freely in treatment of this disease, often proceeding to the point of keeping the patient mildly inebriated during a critical period such as when gangrene is impending. Wright (1940) said that unless there is a definite contraindication—severe diabetes, gastric ulcer—all patients with this disease should have some alcoholic beverage each day for the remainder of their lives. De Takats *et al.* (1939), while not denying the salutary circulatory effects of alcohol, deplored the fact that these patients not infrequently become habitual drunkards.

Foreign Protein Fever Therapy.—Any of the fever-producing methods (see Neurosyphilis) are employed, but principally typhoid vaccine. Wright (1940) aims at obtaining a rise in oral or rectal temperature of 2° or 3° F. (1° or 2° C.) without a chill. His first dose is 5,000,000 organisms, and injections are given every three days provided that the effect of the preceding one has completely worn off. Increases of 3,000,000 to 5,000,000 organisms are made whenever the reactions are not satisfactory, decreasing by the same amounts if the temperature has exceeded 103° F. (39.5° C.) and a chill has occurred; with most patients the top level at which treatments have continued for long periods has been between 70,000,000 and 130,000,000 organisms. Treatments are suspended during acute infections or other serious illnesses. Wright does not nowadays employ stock typhoid vaccine but rather one which is specially prepared for him and which he believes permits of more accurate measurement of dosage. Allen (1939), of the Mayo Clinic, like Wright, considered this the best of all treatments in many cases.

Sodium Chloride Intravenously and Desoxycorticosterone.—The intravenous injection of 5 per cent aqueous solution of sodium chloride, introduced by Silbert in 1923, is the only one of the salt injection types of treatment that has held its own against all the other methods of treatment. The solution is prepared in freshly distilled water, filtered and sterilized at once. The initial injection is 150 cc., all subsequent ones 300 cc., taking about ten minutes for completion. The patients remain ambulatory and can get up at once after

each injection; there are no reactions if the solution is properly prepared, though during injection the patient frequently feels very warm and thirsty. Injections are at first given thrice weekly, then twice, then at increasing intervals as improvement occurs. Duration of treatment—disappearance of symptoms or maximum possible improvement—is from six weeks to two years. In 1935, Silbert reported that he had treated 524 patients by this injection method, with improvement in 83 per cent of the cases and amputation in only 7.6 per cent, among whom about half had persisted in smoking against advice. Wright (1940) seemed to consider this the treatment of second choice, typhoid vaccine being the first (see above).

Sirota (1943) reasoned that a greater secretion of adrenal cortical hormone should increase the blood sodium chloride, increase blood volume and lower blood viscosity and therefore should, within limits, have the same effect in thromboangiitis obliterans as does intravenous hypertonic sodium chloride solution. He therefore tried intramuscular injections of desoxycorticosterone acetate in dosage of 10 mg. once or twice weekly for periods of one to seven months in a small series of cases; the results were sufficiently encouraging to warrant further study.

General Routine.—Rest in bed for a month or more is imperatively necessary in every case no matter in what stage it is first seen, and when improvement takes place the return to partial activity should be extremely gradual. The patient should wear ample underclothing and socks in winter and perhaps even woolen stockings up over the knees; fleece-lined shoes when outdoors and loose woolen socks in bed add greatly to the comfort of many individuals. Heat to promote collateral circulation is employed, either by means of the electric pad or the electric bulb cradle, or by any other means through which heat at or slightly below the temperature of the body may be applied to the affected extremity continuously for a long period of time. Overheating will only increase the pain and is extremely likely to initiate the breakdown of the tissues, as indeed is any other type of trauma; these patients should take even greater care of the feet than diabetics, if such a thing is possible. At the Post-Graduate Hospital in New York, Wright (1940) and his associates gave up the use of contrast baths and also wet dressings, but they employ sitz baths at about 100° F. (37.8° C.) for fifteen to thirty minutes once or more each day if there is no open lesion and soaking of the limb with an open lesion in boric acid solution or physiologic saline solution at the same temperature. A warm cradle is employed to prevent chilling after these treatments. Wright, at the time he last wrote on the subject, was absolutely opposed to the use of heat lamps, diathermy or short-wave machines.

Passive Vascular Exercise (Buerger Method).—The original description is still the model: "The affected limb is elevated, with the patient lying in bed, to from 60 to 90 degrees above the horizontal, being allowed to rest upon a support for from thirty seconds to three minutes, the period of time being the minimum amount of time necessary to produce blanching or ischemia. As soon as blanching is established, the patient allows the foot to hang down over the edge of the bed for from two to five minutes, until reactionary hyperemia or rubor sets in, the total period of time being about one minute longer than that necessary to establish a good red color. The limb is then placed in the horizontal position for about three to five minutes, during which time an electric heating pad or a hot water bag is applied, care being taken to prevent the occurrence of a burn. The placing of the limb in these three successive posi-

tions constitutes a cycle, the duration of which is usually from six to ten minutes. These cycles are repeated over a period of about one hour, some 6 to 7 cycles constituting a seance."

The number of seances per day varies for individual patients.

Passive Vascular Exercise (Oscillating Bed Method).—In a few hospitals there are special beds in which in effect the Buerger exercises can be performed without any active participation on the part of the patient—the bed does the whole thing except pay the costs, which unfortunately limits the usefulness of the whole business.

Passive Vascular Exercise (Machine Method).—Landis and Gibbon (1933), and Herrmann and Reid (1933), independently devised apparatus for the treatment of chronic occlusive arterial disease through promoting peripheral blood flow by alternate suction and pressure applied to the affected extremity. The method has had enthusiastic trial, but the results in Buerger's disease have not been good in the hands of groups other than the originators. Wright (1940) gave it up entirely, and De Takats *et al.* (1939) so thoroughly qualified the indications for its use that I am unable to state them clearly here except to say that the class of patient who profited most in their experience was the one still so little affected by the disease that he was unlikely to present himself for treatment. The apparatus is noisy and often causes the patient much discomfort.

Intermittent Venous Hyperemia.—Collens and Wilensky (1936) applied a pneumatic cuff to the proximal portion of the affected extremity to create alternating periods of venous congestion and release. They described excellent results in a large number of cases. Kramer (1939) reported good results in 6 of 21 patients. Wright (1940) and associates gave the method a thorough trial and then gave it up.

Peripheral Nerve Block.—For relief of pain the peripheral nerves are blocked by alcohol injection, crushing, or section with immediate suturing. This is in no way a specific treatment and is employed only as a palliative measure, but it is said to obliterate pain completely in nearly all instances; it does not relieve intermittent claudication. By the time regeneration occurs, in about a year, arrest of the disease will have taken place if the other elements of treatment have been successfully applied. Walking is not interfered with by these operations (which are simply performed) but the wound surfaces become anesthetic and can therefore be painlessly cleaned and dressed. De Takats *et al.* (1939) finally dropped the crushing operation because of many anatomic variaations, very painful paresthesias during the period of returning sensation, and the loss of defensive reactions in the denervated areas. Perlow and Halpern (1939) preferred peripheral nerve injection with procaine in oil.

Sympathetic Ganglionectomy.—Adson and Brown (1932–1936) found that quite considerable improvement resulted from the performance of sympathetic ganglionectomy in 83 per cent of their 104 patients (100 patients plus 4 who had both upper and lower extremity involvements). My impression is that most surgeons of experience in the disease do not believe that such results are obtainable in the ordinary run of cases, that is to say, that perhaps a preponderance of relatively early cases was seen during the period at the Mayo Clinic. However, Smithwick (1940) obtained "excellent" results in 22 instances in 52 operations on 30 patients and "improvement" in 27 other instances. De Takats *et al.* (1939) claimed success in 49 instances in 56 operations on 21 patients, but their criteria of suitability for operation are the following:

absence of acute inflammatory stage, below forty years and with definite collateral reserve, poor response to conservative therapy. Horton, reporting the Mayo Clinic statistics in 1938, showed that of the 193 patients given sympathectomy, 26 per cent later underwent amputation. He said: "It is well recognized that sympathectomy does not cure thromboangiitis obliterans. Probably it does not even alter the course of the disease in the blood vessels. It does, however, bring about the maximal blood flow to the sympathectomized extremities and for that reason is still the most logical surgical procedure in properly selected cases for increasing the blood supply." The operation is a formidable affair for both surgeon and patient and seems to be attended by a mortality of about 4 per cent in the best of hands.

Miscellaneous Drugs.—Five to 15 grains (0.3–1 Gm.) of *potassium iodide* are given twice or thrice a day during the whole period of treatment by many physicians, but it is doubtful whether structural changes in the vessel walls, reduction of the viscidity of the blood, or hastened absorption of the nonspecific cellular exudates actually follows upon its use. I am convinced that the various *tissue extracts* are still in the experimental stage, for the results do not seem to be striking, and above all they are not uniform, in the specialized clinics in which these studies are being pursued (see Fatherree and Hurst, 1942, and Duryee, 1943, in the Bibliography). There have been reports of the effective use of all of the following agents, but a detailed description of the methods does not seem warranted in the case of any of them: *mecholyl*, *prostigmin*, *papaverine*, *nitrites*, *xanthines*, *testosterone*, and of course *thiamine* (*vitamin* B_1).

Treatment at Soap Lake.—At Soap Lake in the state of Washington there are a body of water which has been claimed to have miraculous power for the cure of Buerger's disease. Allen and Kvale (1943) stated that Fatherree, who was director of the Research Hospital at the Lake, was a former student and assistant of theirs and is perfectly familiar with problems of peripheral circulation. According to Allen and Kvale, Fatherree's studies revealed that the taking of the water internally had no appreciable effect on the peripheral circulation. For the rest, the treatment there consists in baths taken in the water of the lake, varying amounts of rest and exposure to the sun, and daily dressing of the ulcerative and gangrenous lesions by the patients themselves; in addition patients frequently soak their feet in the lake water in the treatment of the ulcerative and gangrenous lesions. Fatherree found that 66 per cent of the patients had recurrent superficial phlebitis prior to their residence at Soap Lake and 62.5 per cent had recurrent attacks during residence; 91 per cent had gangrene, ulceration, or both, prior to residence, whereas such lesions developed among 53 per cent during their residence; 18 patients had either ulceration, gangrene, or both, on arrival and 68 per cent of these obtained healing in an average time of 8.5 months after arrival; 50 per cent of the patients had undergone amputation prior to their residence at Soap Lake and 31 per cent underwent amputation while there. Fatherree's conclusions were said to have been that the majority of patients continued to have active manifestations of Buerger's disease after considerable periods of treatment at Soap Lake and that the treatment was not specific for the cure of the disease; however, he ascribed the popularity of Soap Lake to the fact that 66 per cent of all ulcerative or gangrenous lesions which the patients brought with them to the Lake healed while they were there.

VARICOSE VEINS

Varicose veins of the legs develop principally in women in the early childbearing years, but in some instances they make their appearance at adolescence or at the menopause. The incidence is much lower in men. The varicosities are usually only on the inner aspect of the calf and thigh and the inner and posterior aspects of the knee, but in advanced cases they are present on the posterior and outer aspects of the limb also. The veins appear as tortuous bluish cords beneath the skin that is often atrophic, shiny and pigmented; sometimes there is associated secondary telangiectasia (dilatation of capillaries). Some patients present doughy induration of the ankles. Lymphedema, erythema and eczema are common, but the most serious complications are phlebitis and the sluggish chronic varicose ulcer which appears on the lower third and usually inner aspect of the leg and tends to attain very great size. This ulcer is accompanied by marked inflammation and tenderness and has sloping edges and a coarse granulomatous exudate, in contradistinction to the luetic ulcer with its punched-out edges and serous exudate, and the tuberculous ulcer with undermined edges and a grayish necrotic exudate covering the base. The subjective symptoms of varicose veins are a feeling of weight in the legs and dull aching pain, which is much relieved when the patient lies down or elevates the legs on a chair. Chapman and Asmussen (1942) offered evidence that circulatory efficiency is decreased by the pooling of blood in varicose veins and that undue fatigue, shortness of breath, dizziness, fainting and even precordial distress may be thus occasioned. Spontaneous disappearance of the varicosities does not take place. There seems to be an hereditary tendency toward development of the disease, but its real cause remains unknown.

THERAPY

Walking exercise favors venous return but standing is very bad for these patients. Great care should be taken to avoid even the slightest injuries to the legs as trauma favors the development of ulcer, but unfortunately just the class most often afflicted with varicosities, *i.e.*, the laboring class, can least afford to heed this admonition seriously. The wearing of elastic stockings, or the employment of the woven elastic bandage of the ace type, brings considerable relief to many individuals; tight garters and girdles should not be worn. The legs should be elevated during every moment that it is not absolutely necessary for the patient to be standing. The reduction of obesity is probably of advantage.

Choice of Patients for Injection Treatment

The venous system of the lower limb is divisible into three parts: (*a*) the deeply situated femoral and popliteal veins and their tributaries; (*b*) the superficial internal saphenous vein and its tributaries, serving the front and inner aspect of the leg and thigh and joining the femoral in the foramen ovale; and the short saphenous vein, coursing superficially on the back of the leg to join the popliteal vein at the upper border of the popliteal fossa; and (*c*) the communicating system of veins between the deep and superficial systems. Now since the substances used for injection of varicose veins provoke injury and adhesion of the vessel walls, *i.e.*, occlude the vessels, it is obviously of greatest importance to determine if the deep venous system is intact and functioning well before any part of the superficial system is destroyed. The method by

which presence of full patency in the deep system is determined is called "Perthes' test": obliterate the superficial system with a blood pressure cuff over the foramen ovale and have the leg exercised; deep patency is indicated by emptying of the varices and absence of subjective symptoms, obstruction by dilatation of varices and pain. (Swinton sends the patient around the block with an Ace bandage obliterating the superficial circulation; if she comes back with the bandage in her hand he considers the deep circulation not competent.) Injection treatment is not to be given individuals whose deep venous circulation is impaired. In addition, the following seem to be definite contraindications within the limits specified: (1) active or recently subsided phlebitis; (2) any condition causing the patient to be bedridden; (3) saline solutions should not be used in nephritics, and sugar solutions not in diabetics, otherwise, weighing each case with judgment, such patients may be injected; (4) in cardiac decompensation, injection is usually contraindicated, but Swinton points out that mild cases are sometimes helped—Horlick (1935) said that the multiple injection method should not be used in such people because it is too tiring; (5) advanced age in itself is not a contraindication nor is peripheral arterial disease apparently, but in the latter cases the arterial rather than the venous disease usually demands preferential treatment; (6) the dictum that injections should not be made during pregnancy was first challenged by McPheeters, and more recently by Cheatham and Peck, and by Nicholas; Swinton does not consider it an absolute contraindication, even to the injection of vulvar varices; Edwards also injects such varices, which frequently cause much annoyance and may rupture during delivery, but he admits that after term the engorged veins of the lower extremities and vulva may greatly diminish in size; quinine solutions are not to be used during pregnancy, of course; (7) infectious processes anywhere in the body, even the common cold, contraindicate the treatments by common consent, but some men go so far as to include such a large list of focal infections as would practically eliminate three fourths of the candidates, I should think; (8) neurotics stand these treatments, like everything else, very poorly; (9) D'Abrèu found evidence of thrombosis of the inferior vena cava in 2 patients who told him nothing about the tortuous veins on their abdomens—to avoid the disaster which would probably attend injection in the lower limbs in such cases, he advises routine scrutinizing of the abdomen in all patients.

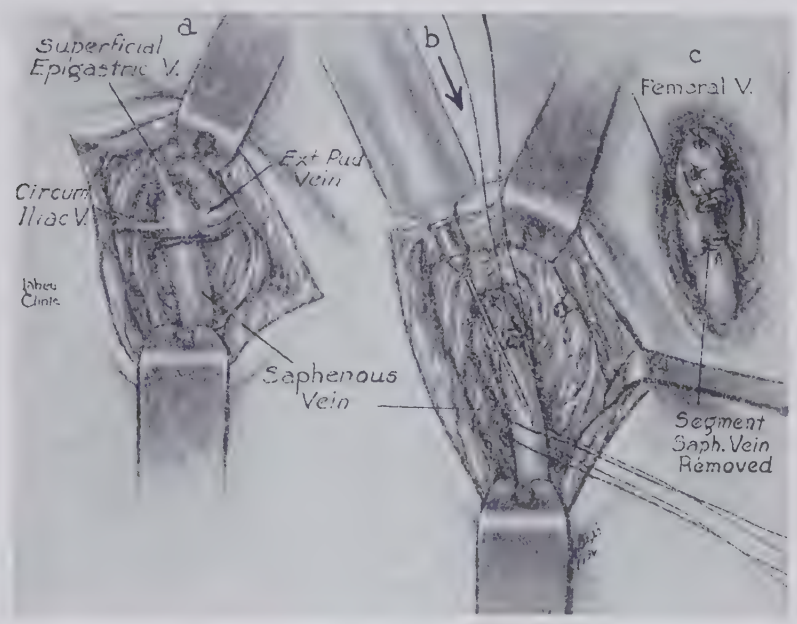
Ligation Preliminary to Injection

Despite the enthusiasm for injection to the exclusion of all other methods of treatment, which has gripped the profession since about 1920, admission is being forced that recurrences are encountered with embarrassing frequency. Reexamination of the anatomic and physiologic bases on which the treatment rests indicates that the fault usually lies in the existence of incompetent valves in the internal saphenous system, allowing a reversed flow of blood from the saphenofemoral junction; such downward coursing blood will recanalize the sclerosed varix and dilate a collateral or redilate a varix below. Recognition of this fact is causing many conservative men to turn back to preliminary ligation of the internal saphenous vein at the saphenofemoral junction in selected cases, the basis of selection being a positive Trendelenburg test: lay the patient flat, elevate the leg and assist emptying of the varices by gently stroking toward the foramen ovale; then make pressure with the finger on the foramen and stand the patient up quickly; the varices will begin to refill slowly

from below, but when the finger is released filling takes place rapidly with blood which is seen to shoot downward from above.

The technic of preliminary ligation and massive retrograde injection of the upper saphenous system, as practiced at the Lahey Clinic of Boston, was described as follows by Swinton (1936), who kindly permitted me to use his illustration:

"The patients are admitted to the hospital the night before operation, the groin carefully prepared as for any surgical operation and usually the entire perineum shaved. In many of the very obese patients it may be safest to continue this preparation for one to two days until the area is clean. Many of these cases are done under local anesthesia yet we prefer in the good risk patients to use cyclopropane, as there is less distortion of the tissues and less



Method of performing a retrograde injection of a sclerosing solution into the internal saphenous system at the time of the ligation of the saphenous vein. Note that all branches and the internal saphenous vein itself have been ligated before the injection is done. (Swinton, N. W.: Surg. Clin. N. A., 16, 1723, 1936; by permission of author.)

discomfort to the patient. A transverse incision is made parallel to Poupart's ligament about 1 cm. below it, continued medially from the femoral artery, which can always be palpated. The saphenous vein will be found immediately beneath the superficial fascia. The dissection of the saphenous vein is then carried up into the junction with the femoral and all the tributary veins in that area are exposed. These high branches must be ligated if the procedure is to be successful and emphasis is to be laid on this careful high dissection. The superficial epigastric vein, the superficial iliac circumflex and the superficial external pudendal are quite constant, empty into the internal saphenous within the last 3 cm. of its course and must be ligated with the main trunk of the internal saphenous if all back pressure is to be eliminated and the setting up of a collateral circulation in that region avoided. After the veins have all been carefully identified the tributaries are divided. The main trunk of the saphe-

nous is then ligated ½ to 1 cm. from the femoral but not divided. At this point we perform a retrograde injection of the entire system with one of the milder sclerosing solutions. We believe this is also a distinct advance in the injection treatment. Varices in the thigh are frequently difficult to locate because of fat, the thigh in many women is very sensitive and we find that following the retrograde injection further injections into the thigh are seldom necessary. We employ a solution of 10 per cent saline combined with 30 per cent glucose for this massive injection. The amount required is variable but ordinarily 10 to 20 cc. is sufficient to obliterate all the veins down to the knee. We have used 40 cc. and thrombosed the entire saphenous system down to the ankle but we do not believe this is a safe amount. Following the retrograde injection a second ligature is placed on the saphenous 1 to 2 cm. below the first and the intervening section of vein removed. We feel that it is somewhat dangerous to divide the vein before completing the dissection as these vein walls are frequently very thin and slight traction on such a stump could very easily tear into the femoral itself. Ace bandages are then placed about the leg at least to the knee. The patients are discharged from the hospital the following day and usually return to work after a total disability of two to four days. Following operation the patients are urged to take a few steps each hour. After a general anesthetic this may be delayed a few hours but all patients have taken a few steps by the evening of the operation. Subsequent injections can be done at the convenience of the patient. . . . They may be started as soon as the patient is discharged from the hospital. There is probably slightly less discomfort if they are delayed a week following the operation. We have found that smaller amounts of the solution are advisable following preliminary ligation at each treatment than we used formerly when the vein had not been previously ligated. . . . Many fewer injections are required where the vein has been ligated previously and most cases can be cleared up in 3 to 6 visits that formerly took two to three times that many injections. A word of caution should be said about discharging these patients. We ask these patients to return for examination and tell them that 1 to 2 further injections may be necessary one month after the completion of the first series of injections, then three months later and again at the end of one year. Only in this way do we feel that all the varices will be found and obliterated."

I think the fact should be stated here that at least two men of vast experience in the injection of varicose veins, Isaak (1940) and Hayes (1941), expressed the opinion in no uncertain terms that the mortality is much higher following ligation and retrograde injection than following injection alone. If this is true, the general practitioner is in the safer camp for most of the ligations are still done by surgeons or specialists in peripheral vascular clinics.

Choice of Sclerosing Solution

Of all the large number of competing agents I shall include here only those few with which most experience has been had. *Sodium morrhuate* has apparently most nearly filled the ideal requirements and has supplanted all other agents in a large majority of clinic and private practices. It is used in 5 per cent solution in a quantity of 0.3 to rarely more than 3 cc. at any one site (in using the multiple injection method—see below—Horlick finds a total of 10 cc. in 0.25- to 0.5 cc. individual doses suitable in average cases). It causes very little pain on injection and severe and lasting after-pain in only an occasional patient. Sloughs are rarely reported as a result of injection outside the vein, and such

as occur do not seem to be so serious as those caused by quinine and salicylate. Occasionally the injection causes a reaction with thickening, tenderness and discoloration around the veins; this reaction, extending as it does for some distance along the course of the vein, is very alarming but it usually subsides in a few days; Cooper (1934) said it presages an excellent result, but I doubt if all observers are convinced of this. Further, dermatitic and urticarial rashes of a nature very suggestive of allergic reactions have been reported, as also severe general shocklike states, 1 case of very alarming bradycardia, and a number of instances of fatal pulmonary embolism, the latter having been reviewed by Vaughn and Lees (1942). But none of these systemic reactions is seen with great frequency. Monoethanolamine oleate, proposed as a substitute for sodium morrhuate by Meyer (1938), already has one allergic type of death chalked up against it, but it is only fair to say that Golden and Heyerdale (1940) stated their belief that the number of severe reactions and even deaths due to sodium morrhuate is considerably greater than the record indicates. Weismann and Heyerdale (1941) suggested the injection twenty-four hours ahead of time of 0.5 to 1 cc. of either of the solutions as a test dose; in the rare instances in which the patient manifests a systemic reaction the hypodermic injection of epinephrine will control the situation. *Quinine hydrochloride with urethane* is available in 2-cc. ampules, which is the top dose that may be injected in one site or at one sitting; the frequent occurrence of cinchonism would seem to indicate a 1-cc. maximum as safer (immediate reaction: tingling, cyanosis, edema, bronchial spasm—antidote: epinephrine; toxic reaction, usually occurring after several hours: tingling, neuralgia, vertigo, visual and aural disturbances; delayed reaction, after several days: malaise, itching eruption, fever, protracted course). Quinine does not cause injection pain or cramp or after-pain, but it does cause slough outside the veins. Schmier (1937) also charged it with being chief offender in production of the slough which sometimes appears several weeks following the injection of a thin-walled vein, a type of "postobliterative" slough which is said not to be due to perivenous infiltration. Menorrhagia, premature menstruation, and bronze discoloration of the skin are recorded against the drug also. *Sodium salicylate*, used in quantities of 1 to 5 cc. of 20, 30, or 40 per cent solution, causes severe pain on injection and slough if injected outside the veins. Occasionally it also causes more or less severe salicylism. *Sodium chloride* is used in 15 to 30 per cent concentration and in amounts from 1 to 10 cc. It causes severe cramp on injection and slough outside the veins, but Schmier has known patients who preferred this brief cramp, which is less severe than that caused by salicylate, to the long drawn out pain sometimes induced by morrhuate. Some men, however, find the salt altogether too variable in its sclerosing effects. *Invertose*, *sucrose* and *dextrose* are used in concentrations of 50 to 75 per cent and amounts of 2 to 10 cc. or more. Systemic reactions are not to be feared with these sugars, but they do give rise to some pain on injection and will cause slough outside the veins; their sclerosing effect does not seem to be uniformly obtainable.

Technic of Single Injection Method

A 5- or 10-cc. syringe with a sharp, short-bevel, 22 to 26 gauge needle is used. Most injections have been given with the patient sitting on a table or standing on a chair in order to have the fullest possible distention of the vein. Time has shown that there is no advantage in segregating a portion of the

vein; the site is merely selected, the skin treated with an antiseptic, the needle introduced and the plunger withdrawn to be sure that the vein has been entered, and the injection slowly made (some men like to express the blood upward before, and hold it out of the way during, the injection). Afterward a tight bandage is placed over the site—McPheeters (1943) said that the importance of this cannot be overemphasized—and the patient instructed to indulge in no rubbing or massaging. Injections, usually made at intervals of one week, begin with the distal veins and work upward (except when there is ulcer—see later). Smith (1941) reported the average number of injections in a series of 491 cases as 8 per individual. In the intervals between injections it is usual to keep a spiral elastic bandage on the limb; the patient is of course to remain ambulatory.

If it is suspected during the injection that fluid has escaped from, or been placed outside, the vessel, injection must cease at once and 5 to 10 cc. of 1 per cent procaine solution should be immediately injected subcutaneously. The injection of 5 cc. of the patient's own blood from a neighboring varix has also been recommended as diluent and to aid absorption through the inducing of marked hyperemia; I do not know how well this works. Dry heat may also hasten absorption. If slough occurs it is said to be best to excise it early—*in the operating room, not in the dispensary or office.*

Latterly, the empty-vein technic has gained many adherents, McPheeters (1943) being perhaps one of its staunchest supporters. The steps are (*a*) apply a soft rubber tourniquet proximal to the site for injection with the patient standing (Bennett-Jones, 1936, places the blood pressure cuff on the lower third of the thigh and inflates to 180 mm.); (*b*) then have her lie down and place the heel on a small block or box; (*c*) when entry is made the tourniquet is released and the injection made after the vein visibly collapses; (*d*) the limb remains raised until the elastic bandage is applied.

Technic of Multiple Injection Method

In an attempt to shorten the total time of treatment many points along the course of a vein are injected at a single sitting. Horlick (1935), who slightly modified McPheeter's original technic, proceeds as follows: "The patient is placed in an erect position and the points where injections are to be made are marked with mercurochrome solution or tincture of iodine so that one may know where to inject when the veins are subsequently collapsed. The patient lies down and the extremity to be treated is elevated and stripped of blood. Two tourniquets are applied about six to eight inches apart, starting at the foot or ankle. These must not be applied so tightly as to cut off the deep circulation, for serious trouble might ensue from the sclerosing solution finding its way to a corresponding segment of the deep circulation. After this, the leg is lowered and the points previously marked are injected between the tourniquets with the solution to be used. Pads of gauze are strapped over each puncture wound. This done, the distal of the two tourniquets is removed and the leg again elevated and stripped of blood. The tourniquet previously removed is then applied about six to eight inches above the one left in place and the leg lowered. This segment is then injected as was the lower one. This procedure is followed up the leg and thigh until the veins are injected to the groin. The most proximal of the tourniquets is left in place and the whole extremity is firmly and evenly bandaged from toes to groin. The Ace or elastoplast bandage is ideal for this purpose. In our clinic, because the cost of these latter is pro-

hibitive, we use sheet wadding and ordinary bandage with satisfactory results. When the bandage is applied the tourniquet is removed. By this means the veins have been injected while collapsed and have been kept collapsed, as nearly as possible, by the bandage. The resulting thrombi will thus be smaller in diameter. It is advisable to keep the bandage in place until the next visit to the clinic. At the ensuing visit, small varicosed veins, so-called 'pick-ups,' missed at first, may be individually injected without the use of tourniquets. If the veins of both legs were varicosed and only one done at the first visit, the other may be done at the same time as the 'pick-ups'."

TREATMENT OF THROMBOPHLEBITIS

Cases of phlebitis vary greatly in severity from those with negligible local and no constitutional signs to those having attacks of rapidly ascending thrombosis, with marked local inflammatory reactions, high fever and other symptoms of sepsis, and even in rare instances embolism. It is at least the older belief that in cases in which there are constitutional signs the patient should be in bed with the leg elevated and hot boric acid dressings applied; the use of cold dressings or the ice-bag has fallen into disrepute because cold is alleged to promote thrombosis and devitalize tissues—Homans (1938) said that he had seen frostbite from the application of ice-bags. With the subsidence of symptoms, an Unna paste boot or elastoplast bandage or elastic stocking is applied, and the patient cautiously allowed to become ambulatory, recurrence of fever and other general symptoms, or significant changes in the white count and sedimentation rate, compelling return to bed. However, there are some dissenters from this plan of treatment. Wright (1936), who has certainly had abundant experience, believes that if the elastoplast pressure is reinforced by sponge rubber strips placed beneath it along the tender inflamed veins, even patients with fever may be allowed to continue out of bed; indeed, his view is that the more severe the superficial phlebitis the more essential it is to keep the patient ambulatory to prevent embolism and deep thrombosis. Until recently most men in this field have been agreed that injection treatments should not be given in either leg while there is an active area of phlebitis present in one of them, the feeling being that an arbitrary waiting period of six months after subsidence is not a bit too conservative. Latterly, however, there have been a number of dissenters from this viewpoint. For example, Heyerdale *et al.* (1943), of the Mayo Clinic, stated that if the patient's symptoms are limited to mild febrile reaction, dull pain, tenderness, redness and a sensation of stiffness in that portion of the extremity involved, the patient may have the offending veins obliterated satisfactorily by a course of injections instituted at the earliest possible moment. In their practice preliminary ligation and injection are performed, warm, moist packs are applied to the affected extremity postoperatively for the patient's comfort for a day or two thereafter, and then the patient returns at suitable intervals for the further sclerosing therapy. Payne (1936) thought to hasten recovery in extensive cases by excision of the inflamed mass of veins and the overlying adherent skin at the end of a month; but Wright firmly opposed this, and I am sure many others agreed with him. Of course in protracted and recurrent cases a most exhaustive study of the patient must be made, particularly seeking to eradicate foci of infection elsewhere.

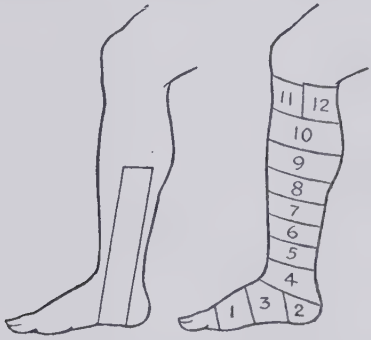
TREATMENT OF VARICOSE ULCER

When I was in residence at the New York Skin and Cancer Hospital a certain number of years ago, we used to treat ambulatory cases in the clinic with salves and no hope, or an occasional Unna paste boot, but when we could get a bed in the house and a patient who could occupy it for the requisite number of weeks or months, we did cure them. The patient was put to bed, the ulcer cleaned, and a gridiron of narrow adhesive straps crisscrossed over it. Various wet antiseptic dressings were then applied continuously in the beginning, and later the exuberant granulations were cut down with the silver nitrate stick, which was also used upon occasion to touch up the sluggish edges here and there. They got well at last (shall I ever forget the old Irish woman who knitted sweaters for the staff, twice round!), but I do not think the dressings had anything to do with the result. The more blithely they went out, the more disgruntled they returned, however, for we were not doing enough with the recumbent position, and in those days we hadn't begun injecting the veins to attack the matter at its roots. Now all that is changed, for the majority of ulcers gradually heal after successful obliteration of the veins (87 per cent in Payne's, 1936, extensive series), and those which do not are apparently in most instances healed by one of the two bandaging methods described below.

The Occlusive Compression Bandage.—The advantages of this method, developed by Wright, in England, are the following: (*a*) the varicose circulation is abolished, forcing blood through the capillaries and thus reestablishing aeration of the tissues; (*b*) edema is reduced, thus bringing the edges of the ulcer closer together and pressing the raised margins of an indurated ulcer down flat; (*c*) delicate granulations and new epithelium are not only protected from dressing trauma, but the wound is actually dressed in its own secretions—the "pansement spécifique" of Besredka; (*d*) pain is abolished in the majority of cases; (*e*) work and exercise aid rather than hinder the cure; (*f*) cure is rapid—"frequently an ulcer of the size of the palm of the hand, if of short duration, will heal within seven days"; (*g*) the ulcer is cleaned more quickly than by antiseptic methods and fetor rapidly disappears; (*h*) varicose veins that had been deeply buried in edema are brought to the surface and rendered injectable; (*i*) the scar is supple without adherence to the bones; (*j*) expense is saved; (*k*) no special training or skill is required to apply the treatment.

Details.—(1) The uppermost veins are injected (Wright uses 5 per cent sodium morrhuate) from above downward. (2) The leg is then wound with an elastic-adhesive bandage (elastoplast) very firmly and evenly, the tightness of the winding being proportional to the swelling and induration, sometimes using practically all of one's strength—"the almost invariable cause of failure is the looseness of the bandage." Begin winding near the toes, having first put in place the stirrup as shown in the accompanying sketch. (3) No treatment of any kind is applied to the ulcer, neither eczema, phlebitis, nor periphlebitis being considered a contraindication; indeed, Wright considers associated arterial disease and diabetes to be practically the only contraindications to the entire treatment. (4) If the ulcer is of the painful type, aspirin powder is blown in with an insufflator and the patient is given a hypnotic for a few nights, the latter not so much for the pain but because "she has fed the ulcer with salves, antiseptics, lint and gauze for so long that she thinks terrible things are happening under the bandage." The pressure over the ulcer, if it is a particularly painful one, is sometimes increased by applying a small firm absorbent felt pad to the ulcer bed and placing another pad of sponge rubber

between it and the turns of the bandage; specially useful is this procedure in treating ulcers in the sulcus under the malleoli where the bandage does not grip very tightly. (5) The patient is instructed to wash off the discharge, if it seeps through, with a nailbrush and soap, and to protect the clothing with a dressing over the weeping area, and also to wear a long stocking over the whole. *Work and as much walking exercise as possible are mandatory.* (6) The subsequent visits are dependent upon the size and location of the ulcer (over the malleoli, movements will loosen the bandage; copious discharge will necessitate frequent changing; disappearance of edema will also require reapplication). (7) Upon each removal of the bandage the veins are injected again in the previous order and also any others that have become accessible, and if the ulcer is large and a good sheet of granulations has developed, grafts are inserted under them on the fibrous bed—insinuation of small implants, darning in threads of skin, or injecting a suspension of skin in saline. "Grafting may be repeated and it is always well to have a graft waiting in the center of the last patch of ulcer to receive the edges as they close in, otherwise there is often an annoying delay at the last." (8) Finally, when the ulcer is healed and all veins obliterated, the former often being accomplished first, an Unna paste boot or an elastoplast bandage is used as long as seems necessary to consolidate the cure.



Wright finds that eczema may develop under the bandage, or if previously present may get worse during treatment; however, so far as the patient will permit, he ignores it and is often rewarded by disappearance of eczema, ulcer and edema simultaneously. Failing, he employs interchangeably bandages impregnated with rivanol 1:1000, ichthyol 5 per cent and aluminum acetate 5 per cent; sometimes he uses zinc oxide ointment. Blisters developing under the bandage do not cause him to alter the treatment; overlapping each turn of the bandage with two thirds of its width, plus the greatest care in application, has usually avoided cutting with resultant linear ulceration in very edematous legs.

Rubber Sponge Supportive Bandage.—This method of therapy developed by McPheeters has been called by him the "venous heart" treatment and rests on the belief that the patient's heart will pump fresh arterial blood filled with oxygen and tissue food to the ulcerated area but that the circulatory apparatus must be artificially aided to carry off the products of combustion and ketosis which cause the local acidosis and tissue death. To this end he applies a rubber sponge tightly to the ulcerated area and then causes the patient to walk a great deal, so that with each step the elastic sponge performs a "systole and

diastole" by which serum, lymph and venous blood are actively pumped away from, and arterial blood into, the affected tissues at the same time that all the advantages of constantly applied firm pressure are obtained. Unless the patient exercises he will suffer intolerable pain; with exercise he will find that the normal soreness and the edema rapidly disappear and "ideal conditions are maintained for the ulcer healing, the end-results are reached in a comparatively short period, and the patient continues on at work during the entire period." The treatment is of course absolutely contraindicated in the bedridden.

Details.—(1) Cleanse the skin and ulcer area with gauze and benzine and apply 10 per cent silver nitrate to the ulcer, which will stimulate but is of no value at the first dressing of a badly infected and necrotic ulcer. (2) Apply some ointment that will *remain soft* to the ulcer, cover it with fluffed gauze and 4 layers of sheet wadding or cellucotton. (3) Bandage in place directly on the ulcer a good grade rubber bath sponge (firmest possible) that is 1 inch larger than the ulcerating area, using a plain 3-inch gauze bandage and being careful that the whole does not slip to one side. (4) Apply a 4-inch Ace bandage from just below the knee to the toes, over the sponge and dressing, applying it as a double figure-of-8 about the foot and ankle. (5) Convince the patient of the absolute necessity of walking as much as possible. (6) The dressings are to be changed as often as necessary to prevent saturation. "Every two days is preferred. The rubber sponge can be boiled up and used again when soiled, but should be discarded as soon as it has lost its 'kick' and has become firmly pressed together." After healing, the subsequent treatment is practically the same as in the method of Wright (see above).

Mecholyl Iontophoresis.—In cases which have been especially resistant to the above types of treatment, or when one of the several contraindications has made injection treatment impossible, several men (Sayler *et al*, 1936; Murphy, 1937; Sokolov and Meyers, 1939; Montgomery, 1941) have reported more or less success by keeping the patient actively ambulatory, using no other dressing than a bit of petrolatum on gauze if it makes the patient more comfortable, and resorting to iontophoresis of mecholyl (acetyl-β-methylcholine) solution. The following is Sayler's original technic: reinforced asbestos paper soaked in 0.5 per cent solution of the drug is wrapped around the foot and leg as high as the knee, the ulcerated area not being covered during treatment until it has acquired a firm scab. A malleable metal plate is placed over the wet paper, not applying it over the ulcerated area, and connected to the positive pole of a galvanic machine; a regular large moist pad electrode, placed under the back, is connected to the negative pole. The current is turned on and slowly increased to 20 to 30 milliamperes and then slowly reduced before turning off; treatments lasting twenty to thirty minutes are generally given two or three times weekly. The local reaction consists in warmth, prickling, blush, gooseflesh, sweating, elevation and fall and subsequent elevation in temperature. A general reaction, with circulatory, respiratory and gastro-intestinal symptoms predominating, may be stopped at any time by an injection of atropine sulfate.

The Unna Paste Boot.—This dressing, several times referred to above, is made and applied as follows: (*a*) Stir 100 Gm. of gelatin into 400 cc. of water and allow to stand overnight; then bring to a boil and add 100 Gm. of zinc oxide and 400 cc. of glycerin which have been previously rubbed together to smoothness; boil while stirring for fifteen minutes. (*b*) Cool to a bearable temperature, or heat to same if the paste has already hardened, and paint with a

wide camel's-hair brush over the ulcerated area, which, together with the leg, should have been thoroughly cleansed first, the latter shaved also. Now apply a spiral bandage and a second coat of paste and repeat until the desired rigidity is attained. The entire space from ankle to knee is usually covered. Isaak (1940) said that the ready-made zinc oxide-gelatin bandages, nowadays available, may be satisfactorily substituted in the above procedure. In the older type of treatment, when the secretion began to seep through, a window was cut over the ulcer and antiseptic and cleansing applications made directly to the raw surface, the leg being held fairly stiffly encased in the paste boot; now, as described above, the Unna dressing is more often applied on the dry surface after healing of the ulcer. When wet dressings are being applied, the boot is usually changed every two weeks, every three weeks at least.

Local Application of Blood, Plasma, Chlorophyll, Tyrothricin.—Naide (1943) treated a small series of ulcers of several types by spraying them with the patient's own blood, there being five cases of varicose ulcer in the group; healing was said to have occurred very well under the blood clot and at even a better rate when there was substituted for blood dried plasma diluted with only one quarter of the amount of distilled water which would ordinarily be used to restore it to the normal concentration of human plasma. Murray and Shaar (1944) obtained healing in 9 of 10 varicose ulcers as the result of the application of a paste made from human red blood cells. Gahan *et al.* (1943) obtained good healing in seven of ten varicose ulcers to which chlorophyll had been applied in one of two forms: the ointment consisted of oil-soluble derivatives of chlorophyll mixed with hydrous wool fat in the proportion of 1 to 28; the aqueous solution was made by dissolving 2 Gm. of a water-soluble derivative of chlorophyll in a liter of distilled isotonic saline solution. Kvale *et al.* (1944) obtained good results in 8 of 15 cases through the application of tyrothricin in solution.

Thiamine for Pain.—In a few individuals the pain of varicose ulcers is very severe and, since one does not dare employ opiates, it is often difficult to give relief; this may be particularly distressing when the ulcer is yielding very sluggishly to treatment. In 10 such patients, Ochsner and Smith (1940) gave thiamine hydrochloride (vitamin B_1) in doses of 3 to 15 mg., in one instance 30 mg., daily; in all but 1 patient there was definite relief in a few days and 8 had complete subsidence of their symptoms; definite increase in the healing of the ulcer was noted also in half the cases. The authors felt from this experience that 5 mg. thrice daily should be the beginning dosage, to be doubled if results are not obtained. No explanation of the action of the vitamin in these cases is at hand.

ESSENTIAL HYPERTENSION

(*Hyperpiesis*)

In 1943, Master *et al.* reported a study of the blood pressures of nearly 15,000 individuals whom they believed to constitute a fair cross section of the urban population of the United States; the number of Jews, whose racial tendency for the development of hypertension is recognized, was felt not to be inordinately high in the group, and the number of Negroes, in whom hypertension is appreciably more frequent than in whites, was much lower than in the total

population—hence it was thought that if the figures erred it might possibly have been in the presentation of findings lower than those truly represented for a cross section of the native population. The findings were very illuminating for they showed that by the most liberal definition of hypertension, 140/90 or over, practically half the male population and 60 per cent of the female population forty years of age and over are hypertensive; the proportions increase rapidly so that among persons seventy and over more than three fourths of the men and four fifths of the women have high blood pressure of this degree. Even by the much more conservative definition of 150/100 or over, about one third of the male population and over two fifths of the female population of ages forty and over have high blood pressure; this percentage also rises rapidly so that it is present in more than a majority of men sixty and over and of women fifty and over. The study revealed such a high proportion of persons over forty with hypertension of slight and moderate degree that Master *et al.* felt there might be some need for revision of our point of view as to what is normal for persons in middle and later life. For example, they felt that if at least half the persons over sixty have a blood pressure of at least 150/90 it can hardly be said that such a degree of hypertension is abnormal, this point of view, however, not in any way conflicting with the fact that pressures below this level are more favorable for longevity. In the end individualization again must be the criterion for prognosis, since while it is undeniably true that hypotension is ideal, other things being equal, clinical experience amply shows that in many persons hypertension is not incompatible with a high degree of mental and physical efficiency over long periods of time. In Flaxman's (1936) statistical study, like the earlier classical one of Janeway, there was revealed a small but significant number of patients still alive five to twenty years after the appearance of the first symptoms.

When the individual with high blood pressure presents himself as a patient—usually between forty and fifty, possibly as likely to be a man as a woman, often broad-chested and obese—the symptoms which lead to the discovery of the hypertension are usually disturbances in kidney function, cardiac and respiratory complaints, vertigo, dyspepsia, bleeding from the mucous membranes, loss of weight, retinal hemorrhage, persistent morning headaches, unusual drowsiness, and transient palsies and aphasia. The height of the systolic pressure varies greatly; it may be only 150 or 160 or it may rise above 300. Of course the height of the diastolic rise depends upon the state of the heart and vessels, hypertrophy and arteriosclerosis being usually early complications of hypertension. Murphy, Grill *et al.* have shown that the histologic quite like the clinical manifestations in "malignant" cases differ from those of ordinary cases in degree only. Rogers and Palmer (1944) found that the transient nervous hypertension, frequently found during physical examinations in War II, had excellent prognosis at least so far as military risk was concerned.

The etiology of the essential hypertension syndrome is still obscure, though great strides have been made in recent years in the study of hypertensive states in experimental animals, Goldblatt and Page and their respective associates being chiefly responsible for these advances. From these studies it seems that the kidney produces a substance, renin, which is converted in the normal blood plasma into a second substance, angiotonin, the latter being an agent which causes vasoconstriction (in the kidney there is particularly constriction of the glomerular efferent arterioles). There is also evidence that the normal blood contains a substance which inhibits the action of this vaso-

constricting agent. There has been much study of the effect of kidney extracts thought to contain the inhibitor agent, but the subject is still in the experimental stage and not ready for general application in practical treatment.

THERAPY

Treatment of this serious malady must remain entirely unsatisfactory until the cause or causes of the rise in pressure are elucidated. The measures to be described below are designed to lower pressure solely in an attempt to prevent the deadly sequelae of a maintained hypertension—heart failure, apoplectic stroke, kidney dysfunction. Evans and Loughnan (1939) made a very careful study of a large number of drugs in comparison with placebos in 70 patients; their results, taking into account the wide "normal" variations of blood pressure in hypertensive patients, of which Ayman wrote a number of years ago, were the following: (*a*) none of the drugs was of value in lowering blood pressure; (*b*) the following only were of value in effecting symptomatic improvement irrespective of the blood pressure, which indeed was often in a high phase at the time: iodides, bismuth subnitrate, bromides, barbiturates and potassium thiocyanate. Kapernick's (1943) study of a large group of drugs also showed that none of them had significant hypotensive effect. However, the interesting studies of Ayman and Goldshine (1941) showed that the patient's blood pressure when taken at home by himself or a member of his family is consistently and considerably lower than when taken by the physician in office or clinic—which would indicate the possibility that our treatment measures are more effective than office records show. Perhaps it is well to point out also that no treatment is often the best treatment, at least for a while, *i.e.*, some patients will only be made unnecessarily miserable instead of being helped if it is hinted to them at all that their blood pressure is high.

Rest and Psychotherapy.—I quote Mosenthal: "The best available means at the present moment to reduce the blood pressure in essential hypertension is to obtain nervous relaxation in the patient. This is glibly said but hard to accomplish, for it means untold effort on the physician's part and limitless cooperation by the patient. Occupation, home life, social obligations and many other factors must be studied and their rough corners rounded off. . . . The regulation of occupation, family relations and other personal affairs must remain an individual matter. It is a good plan to have the patient visit the office once a week and talk over such topics for a few minutes. Eventually a way out may suggest itself. A good routine of relaxation is one or two hours' rest after lunch and at least eight hours in bed at night. In severe cases, one day a week in bed may be recommended. At times, more or less prolonged rest in bed may be of value."

The psychosomatic fellows express about the same thing as the above but in their own weird fashion, which I suppose we must try to understand. Witness Weiss (1942): "A common problem seems to be the presence of emotional tension due to chronic repressed hostility. This inhibited aggression (chronic rage) seems to bear a specific relationship to hypertension and, if it can be turned outward by means of psychotherapy, anxiety is diminished and blood pressure is often lowered. Even if blood pressure is unaffected, the treatment often benefits the patient by making him a healthier and more effective personality."

If nervous relaxation cannot be achieved without drugs, there should be no hesitation in employing the sedatives; see the article on Insomnia. Allen

and MacLean (1940) believed it might be advisable to investigate the value of raising the head of the bed in attempting to prevent the early morning headaches.

Exercise.—Evidence is accumulating that sedentary individuals are more subject to hypertension than physically active persons. Gunewardene (1935) has made the interesting observation that in India hypertensive disease rarely occurs among rickshaw runners with their strenuous exercise and long hours but that it is common in certain social groups who lead sedentary lives with habitual overeating. Many years ago Janeway found that exertion, even as strenuous as in tennis playing, was helpful in younger persons. Mosenthal gave it as his opinion that moderate exercise as walking, golfing or restricted setting-up calisthenics, serves to keep the voluntary and cardiac muscles in better condition and promotes more satisfactory well-being than if a more physically restricted course is pursued. One may guardedly lay down the principle, then, that exercise within the limits of cardiac power is beneficial.

Turkish Baths.—Some hypertensives find that they are greatly relaxed by Turkish baths and therefore enjoy taking them; but the physician must bear in mind that the relative hypotension often suddenly induced by these baths may predispose to thrombotic occlusion of vessels, depression of cardiac vigor and rebound of the arterial tension to a level higher than before the bath. I think it is the consensus among students of this disease that the patient had best forego this indulgence.

Diet.—All the dietary restriction that the hypertensive patient needs is in quantity if he is obese or if there is a gobbling fulsome tendency in his family; for every bit of evidence in favor of any particular *qualitative* change in diet it is possible to find a sufficient amount of recorded contrary evidence to invalidate the whole contention.

Alcohol and Tobacco.—Alcohol in great moderation does not seem to be harmful, indeed it seems to "smooth out" some of these temperamental people. Smoking is sometimes demonstrably harmful.

Cathartics.—Alvarez and associates demonstrated a number of years ago that constipation has no effect on blood pressure in men, and that in women it is associated with lowered pressure; findings which should dispose once and for all of the "intestinal auto-intoxication" myth. That a certain number of patients die in the lavatory is taken to indicate that straining at stool is to be combated at all costs; be it noted, however, that no one has proved this point.

Venesection.—Bleeding as the sheet-anchor of treatment has of course been abandoned but many physicians still resort to it in the plethoric individual when heart failure or apoplexy is threatening. Elliot, who reviewed the subject some years ago, concluded that "a good bleeding will sometimes postpone the breakdown." Mosenthal (1940) expressed himself in favor of frequent moderate bleedings (200–300 cc.) in patients who are inclined to plethora.

Intravenous Injection.—The modern method of depleting the circulation and thus relieving the brain is to inject hypertonic solutions, but the superiority of this method to venesection does not seem to me to have been conclusively shown. *Sucrose* in 50 per cent solution is injected intravenously in an amount of 300 to 500 cc. daily. It seems that diuresis begins in two hours and lasts usually for six hours and that there occurs prompt reduction in spinal fluid pressure with gradual return to the previous level in eight to twelve hours; blood pressure is little affected. Relief from such aggravating symptoms as headache, vomiting, vertigo, twitching and dizziness has been reported

But Anderson and Bethea (1940) found distinctive renal lesions after the administration of such sucrose solutions in 6 cases, and similar lesions have been produced in experimental animals. *Magnesium sulfate* is also injected intravenously, average dosage being 10 cc. of 10 per cent solution not oftener than once daily. Lissner (1934) found these injections exerting a marked influence upon the eye changes, aiding absorption of exudate of retinal hemorrhages and adding hope of prevention of threatened blindness. Murphy *et al.* (1941) cautioned that intravenous injections of any sort must be given extremely slowly in patients with any type of cardiovascular disturbance.

Iodides.—Sodium or potassium iodide, 5 to 15 grains (0.32–1 Gm.) three times daily, is employed by many physicians in all cases even though there is no evidence of a syphilitic involvement. I think we have very little scientific warrant for this sort of routine "alterative" medication, though the statement, "it can't do any harm," is probably a true one. Parkinson and Hoyle (1934) pointed out interestingly that in cases benefited there may be an underlying thyrotoxicosis. However, in the study of Evans and Loughnan (1939), referred to in the beginning of this section on therapy, iodides were one of the small group of drugs that was effective in inducing symptomatic, though not blood pressure, improvement.

Digitalis.—When heart failure threatens or occurs it should be treated just as at any other time. The additional practice has arisen in the last few years of attempting to forestall the cardiac catastrophe by placing the patient on digitalis before the heart shows signs of failing; full digitalization is usually approached very slowly through administration of minimal daily doses (see Heart Failure).

Nitrites.—Erythrol tetranitrate and mannitol hexanitrate are the longest lasting in their effect upon the blood pressure and are therefore to be preferred. They are obtainable in $\frac{1}{4}$- and $\frac{1}{2}$-grain (0.015 and 0.03 Gm.) tablets; the effective dose is $\frac{1}{2}$ to 1 grain (0.03–0.06 Gm.) every four to six hours or as indicated. Both preparations are rather expensive. Weaver *et al.* (1944) found that some of their patients on mannitol hexanitrate obtained striking relief of symptoms even though the drug had not induced a fall in blood pressure.

Sodium nitrite is second in point of duration of effect to the above two salts, but it has the disadvantage of causing gastric disturbances in most individuals. It is given in capsule in a dose of 2 to 3 grains (0.13–0.2 Gm.), often combined with an equal amount of sodium or potassium iodide, at intervals to be determined in each case.

Nitroglycerin is the least durable in its effect upon the blood pressure, but it is the preparation often preferred for the following reasons: it does not usually disturb digestion; it may be conveniently prescribed in the form of hypodermic tablets of 1/100 grain (0.0006 Gm.), which are not volatile, do not quickly deteriorate and may be easily dissolved under the tongue. The dose is one or more tablets as required. The drug is much cheaper than the erythrol or mannitol salts. Lueth and Hanks (1938) reported severe reactions in a number of their patients using nitroglycerine: nausea, vomiting, collapse and the involuntary passage of urine; such reactions are also mentioned under Angina Pectoris.

Amyl nitrite is very little used in the treatment of hypertension because of the brief duration of its action.

Stieglitz found the nitrate radical of bismuth subnitrate liberated as the nitrite radical by bacterial action in the intestine and the nitrite slowly and

evenly absorbed to produce hypotensive action. Bismuth subnitrate is given in doses of 10 grains (0.6 Gm.) three times daily in capsules. Stieglitz (1936) reported very good results in a large number of patients, but both Ayman (1932) and Bruen (1934) were unable to duplicate the findings in rigorously controlled series; Evans and Loughnan (1939), however, in the study referred to in the beginning of this section on therapy, found bismuth subnitrate one of the small group of drugs that was effective in inducing symptomatic, though not blood pressure, improvement.

Thiocyanates (Sulfacyanates).—Sodium and potassium thiocyanates, the latter being perhaps the more frequently used salt, were among the small number of drugs found effective by Evans and Loughnan (1939) in inducing symptomatic, though not blood pressure, improvement, as noted in the beginning of this section on therapy in hypertension. And I know that they are very popular with the profession just now; Ayman (1944) has recently written favorably of them, Koffler *et al.* (1944) have reported appreciable lowering of the blood pressure in about 50 per cent of 39 ambulatory patients and subjective improvement without lowering the blood pressure in some of the others, and Caviness *et al.* (1942) felt that the employment of thiocyanates need no longer be regarded as empirical since they found concentrations of from 0.31 to 2.55 mg. per 100 cc. of blood in patients who had not received the drug. Still, there is the conclusion of Goldring (1943), after 44 trials in ambulatory and 25 trials in hospitalized patients at Bellevue, that thiocyanates should not be administered to hypertensive patients because, apart from their toxic effects, their influence is not striking in either the frequency or the extent of blood pressure reduction and almost any medical or psychotherapeutic measure may be expected to yield results equally effective and with no element of danger. And this statement of Flaxman (1943), which merits full quotation: "When I began work in the out-patient dispensary of the Mount Sinai Hospital, my colleague in the next room (Dr. Henry Siegel), who had preceded me there by 2 years, was employing the thiocyanates for such patients. Therefore, I decided to use only sedatives and to treat the hypertensive patient symptomatically. For the next three years, until he left the dispensary, we continued our separate therapies. On days that he was absent I saw his hypertensives, and *vice versa*. The only difference noted between the two groups was that mine were more comfortable, although his patients had a more pronounced lowering of blood pressure. True, the blood cyanate method was not used, but the length of time the patients were kept on the drug seemed sufficient to determine its value. The personal element could be excluded because of the same placid disposition in both, and we had plenty of time. After he left, I 'inherited' his hypertensive patients, and thereafter followed all of them. As I could still see no real value to the thiocyanates, I do not use them in the treatment of hypertensive patients." And furthermore the following facts seem to me to require most careful consideration:

(*a*) The foremost advocate of thiocyanate therapy, Barker of Northwestern University, freely admits the toxic actions of the drugs, but feels that these actions may be grouped as mild and severe, and that the severe effects are seen only when the proper blood cyanate level has been exceeded.

(*b*) It is considered that the cyanate level at which best effect is obtained is 8 to 12 mg. per 100 cc., that significant toxicity begins to appear at 15 mg. and increases rapidly above 20 mg., but that serious manifestations are not to be expected under a level of 35 mg. Barker's routine, according to Wald

et al. (1939) of his group, is to administer two doses of 5 grains (0.3 Gm.) daily for three days and then do a blood cyanate determination if the patient is in hospital; those not hospitalized are given ten doses within a week and the first cyanate determination is done on the eighth day. But in their experience maintenance dosage varied from 5 grains (0.3 Gm.) a week to as much as 15 grains (1.0 Gm.) a day, and fluctuations in dosage occurred frequently in many cases. Obviously, this means that if the physician is to know at all times the precise cyanate level of his patient—which Barker insists upon—he is obliged to have cyanate tests performed at very frequent intervals indeed.

(*c*) Wald *et al.* listed the following *mild* reactions: sensations of weakness and fatigue which occur in 75 per cent of cases and are said usually to disappear after several weeks; frequent occurrence of aching and cramping of the calf muscles; increased nervousness and irritability in some instances (but sedative effects are also sometimes seen); toxic dermatoses of various sorts (severe exfoliative dermatitis had not been seen by them but it has by others); enlargement of the thyroid; various gastro-intestinal disturbances. As *severe* reactions, seen only when the allegedly safe blood level has been exceeded, they listed: severe gastro-intestinal disturbances; vascular collapse; cerebral thrombosis; slurring speech, aphasia, convulsions and delirium; angina pectoris; death, usually preceded by coma and convulsions.

(*d*) Despite the assertions of the proponents of the use of these drugs that serious reactions are not to be feared if the dosage is such as to keep the blood cyanate level under 15 mg., such reactions have been recorded on low blood levels: (1) Robinson and O'Hare had reactions in 38 per cent of their 75 patients; serious reactions occurred in 6 cases and in 2 of these within the "safe" level; (2) Greene and Snow (1939) reported a very severe reaction in a patient who had been on the drug only a few days and had not had a level above 3.7 mg.; (3) The fatal reaction in Garvin's (1939) patient began when the cyanate level was within the safe range, as it did also in the patient of Solomon *et al.* (1943); (4) Blaney *et al.* (1941) found toxic manifestations common above 15 mg. but not invariably present even with twice this concentration, while in 1 of their 20 patients serious intoxication occurred at a concentration between 6 and 7 mg.; (5) Blaney *et al.* examined their data for criteria to aid in the selection of patients suitable for thiocyanate therapy, including considerations of age, duration of hypertension, sex, severity of hypertension, cardiac and renal complications, retinitis, test of vascular reactivity; they found nothing that would seem to serve as a useful guide.

Miscellaneous Drugs.—I do not feel, from close study of the rather large literature available to me, that any of the following have yet been shown to have worth in hypertension: histamine, acetyl-β-methylcholine (mecholyl), adenosine and adenylic acid, tissue extracts, cucurbocitrin, estrogenic substances (diethylstilbestrol, etc.), androgen (testosterone), oxygen, vitamin A.

Surgical Procedures.—In the preceding edition of this book I stated my feeling that the surgical treatment of essential hypertension did not rest upon a sound scientific basis. The surgical literature of the subject has now become rather bulky, but my opinion in the matter—purely "armchair" to be sure—has not changed. Even when considerable lowering of blood pressure is obtained it is notorious that the effect is often temporary. Flaxman (1944) compared his series of 244 medically treated cases with 350 cases treated surgically by one of the groups specializing in this work; a study of the mortality revealed very little difference between the two groups. Indeed, it seems to me highly

entertaining that Volini and Flaxman (1939), at Cook County Hospital, found that the symptomatic relief and blood pressure reduction resulting from nonspecific surgical measures (*i.e.*, hysterectomy, prostatectomy, cholecystectomy) in the presence of essential hypertension are similar to and sometimes better than those resulting from specific surgical measures (*i.e.*, extensive sympathectomy, splanchnic nerve resection, celiac ganglionectomy). The newest surgical approach is unilateral nephrectomy; Sensenbach's (1944) study and review may be summarized as follows: (*a*) only 5 of the 75 cases of hypertension in the literature met the requirements for cure after nephrectomy, since approximately one third of the patients had a fall in blood pressure to normal levels but had been followed for less than two years, one third had a reduction in blood pressure but remained hypertensive, and in one third the blood pressure was unchanged or increased; (*b*) cases in which unilateral nephrectomy is indicated are rare; (*c*) the removal of a kidney, if it retains any function at all, is likely to increase the severity of the hypertension rather than to decrease it, even though the function of the opposite kidney is entirely normal.

ARTERIOSCLEROSIS

Arteriosclerosis is a disease characterized by hyperplastic, hypertrophic, fibrotic, calcareous and necrotic changes in the vessel walls, resulting ultimately in diminution of normal elasticity plus weakening and deformity. Apparently many individuals can remain in excellent general condition with tortuous and quite "hard" arteries, but they carry always the potentiality of experiencing a vascular crisis—cardiac, cerebral, gastro-intestinal, peripheral, and so on. Until such accident occurs, the following are about the only aids in determining the state of an individual's arteries: (*a*) a gradual loss of mental and physical vigor in an elderly individual otherwise apparently healthy is looked upon as presumptive evidence of generalized arteriosclerosis; (*b*) if ophthalmoscopic examination reveals normal or nearly normal retinal arteries, and if there is extensive drop in diastolic blood pressure upon inhalation of amyl nitrite (Stieglitz test), one may assume that there is very little hardening of cerebral vessels; (*c*) arteriographic and oscillometric studies may make possible the differentiation between vasospasm and organic arterial disease in the peripheral vessels; (*d*) intermittent claudication—pain in the calves, produced by exercise but not by standing, and relieved by rest—is indication of advanced arteriosclerotic or thromboangiitic occlusive involvement in the extremities.

In most cases the blood pressure is not raised, but when it is, that is to say, when essential hypertension and arteriosclerosis are coexistent, then the prognosis is much more grave. The following is the order of frequency with which most pathologists have found the organs to be affected, those organs most frequently affected being also most markedly affected: spleen, brain, kidneys, adrenals, pancreas, heart, gastro-intestinal tract, lungs, liver and diaphragm.

Some investigators are beginning to state in a tentative fashion that a definite hereditary factor is responsible for the development of this condition in some individuals much earlier than in others living under the same stress and strain. Diabetes appears with suggestive frequency in connection with this disease, but what direct relationship it or any other factor such as the alleged disturbance of cholesterol metabolism has to do with the etiology remains unknown.

The great anatomist Scarpa (1747–1832) was the first to record the opinion that arteriosclerosis is a disease of the inner coats of the arteries.

THERAPY

For those victims of arteriosclerosis who suffer general mental and physical deterioration there is nothing to do save direct their lives in as pleasant channels as possible; nor can one write much of an edifying nature about the prevention of the condition. To avoid the competitive hurly-burly of life as much as possible, to avoid too quick returns to full activity after attacks of the acute diseases, to submit to the fullest treatment for the chronic affections, and to select one's parents as carefully as may be, are all measures of presumptive value. No form of dieting, not even that type which is called "low-cholesterol" (omit brains, butter, egg yolk, fish and fish roe, kidneys, lard, liver, meat, oysters, poultry, suet and sweetbreads) is rationally indicated. In effect the treatment of localized arteriosclerosis is really the treatment of chronic nephritis, coronary thrombosis, congestive heart failure, hemiplegia, etc.—entities dealt with elsewhere in the book. Where there is intermittent claudication and peripheral vascular occlusion with gangrene, the treatment is essentially the same as in thromboangiitis obliterans, except that elderly arteriosclerotic patients may be expected not to tolerate typhoid vaccine injections so well as the younger patients with Buerger's disease, and one would think that radical operation should be approached in this group with great diffidence. Doane and Adlin (1944) reported one case of intermittent claudication relieved by thyroidectomy, but it is not often that a single swallow has made a summer. Bernheim and London (1937) found cessation of smoking equally demanded in the peripheral vascular occlusion of both arteriosclerosis and thromboangiitis obliterans. It is possible that in arteriosclerosis one or other type of passive vascular exercise may finally be shown to be of somewhat more value than in thromboangiitis obliterans, but so far I have seen no published study proving this to be so in a large series of cases. Gootnick (1943) obtained complete relief from the severely painful calf muscle cramps which often afflict arteriosclerotic patients in bed at night by the administration of quinine sulfate at bedtime; in most of the patients 3 grains (0.2 Gm.) suffice. Many of us who do not admit at least that we are arteriosclerotic also occasionally have a painful cramp of this sort and have learned to relieve it by forceful dorsal flexion of the foot and to prevent recurrence by avoiding extension of the foot when stretching; perhaps these simple things would be helpful in arteriosclerotics also.

HEMIPLEGIA

The three chief causes of hemiplegia are hemorrhage, embolism and thrombosis, but it will be convenient to include at this place also a few measures more particularly applicable to paraplegia due to severe cord injury. Whether the patient has bled or is bleeding at the time he is first seen in a typical "stroke" is by no means easy to say, but it is the time-honored custom to assume that hemorrhage is occurring and that something must be done to stop it. To this end it is usual to place an ice-bag on the head and lower the feet and place them in a warm mustard bath; if the latter measure is not easily feasible the feet should at least be warmed by the use of hot water bags

or the electric pad. Most patients who have bled sufficiently to have hemiplegia will die very soon and these measures will probably do nothing to stay the end; however, it is little short of cruel to the anxious family merely to stand by and do nothing, and thus these manipulations are amply justified on the basis of the activity and participation of a number of individuals which they necessitate. Another bustling type of treatment is autohemotherapy: withdraw 25 to 30 cc. of blood from a vein and immediately reinject it into the buttock; it is well to have a few cubic centimeters of 25 per cent sodium citrate solution in the syringe as the blood is drawn. Venesection to reduce blood pressure is now discountenanced; lumbar puncture and drainage is probably no more justified, since coma in apoplexy is nowadays thought to be caused largely by cerebral edema which is not remedied by either of these depleting measures. The performance of lumbar puncture merely for the purpose of differentiating cerebral thrombosis from cerebral hemorrhage is not often considered advisable. The use of stimulant drugs is contraindicated. After the cataclysmic event, and whether the patient has or has not recovered consciousness, and regardless of the hemorrhagic, thrombotic, or embolic nature of the acute episode, the therapeutic problems are posed by the residual paralyses and their complicating sequelae. Symptomatic treatment is all that is available in the present state of our knowledge; many of the following measures are really nursing details.

Care of the Skin.—This patient, like any other, is to have a daily soap and water bath. The best way to minimize the damaging effects of sustained pressure upon bony prominences is to have the patient shifted from one position to another—every two hours is not a bit too often. Water cushions, next best air cushions, and lastly cotton rings, placed to advantage, will help distribute the pressure; pillows under the back and knees are also helpful. Sheets and bedclothing should be kept absolutely free from wrinkles and crumbs or other gritty substances; this is very important. In shifting the patient he is to be lifted and not shoved or pulled about. If he has free use of his arms and is assisting in the nursing by pulling on a rope to raise the upper part of his body, Cohen (1935) pointed out that special attention must be given to the skin of the buttocks and lower limbs which are much chafed by such movements. In most instances frequent gentle rubbing of the back with 50 per cent alcohol (not denatured), followed by light application of talcum powder, is good treatment; 1 ounce (30 Gm.) of alum added to the pint (500 cc.) will make the lotion still more drying. But judgment must be exercised for there are cases in which the skin, already excessively dry, will be better treated by the application of an ointment; Fantus (1935) offered the following, which looks very much like a shotgun prescription to me despite its alleged popularity with the nurses at the Cook County Hospital.

℞	Zinc stearate	5.00
	Tincture of benzoin	5.00
	Scarlet red ointment, 5 per cent	0.25
	Hydrous wool fat	30.00
	Liniment of camphor	180.00
	Mutton tallow	500.00

Melt the fats, add the camphor liniment, and, when the mixture has almost cooled, beat in the tincture of benzoin and the zinc stearate until a creamy mixture is secured.

Label: After each cleansing, apply a very small amount of this ointment during the back rub if the skin is harsh and excessively dry (to prevent bed sores).

The application of elastic adhesive plaster (elastoplast), not stretched before applying, or a dressing of flexible collodion to a threatened point is said to prevent sometimes the development of a bed sore. The greatest difficulty lies of course in preventing maceration of the skin in a patient who is incontinent. Several layers of newspapers on top of the sheet (which has a rubber sheet beneath it to protect the mattress), with absorbent material such as oakum between the papers and the body, is the measure usually resorted to; sometimes such a dressing may be held in place diaper-wise. In the worst cases a specially divided mattress may be employed, or a hole may be cut in the mattress at hand and the fluids directed into a pan on the floor by rubber sheeting draped in the hole. In some cases of paraplegia, especially where there has been severe damage to the cord, the patient suffers paroxysms of sweating which of course only add to the dangers of maceration; atropine sulfate, 1/100 grain (0.0006 Gm.) is indicated.

Hofmann (1941) described the satisfactory use of a wagon-bed-like framework of wood, fitted with legs and rollers and filled with sawdust; that portion of the sawdust which is soiled can easily be removed and replaced by fresh, and the whole "bed" can be stirred up daily with a paddle to keep it soft and comfortable. Soft-wood sawdust is of course to be chosen and walnut especially avoided because it stains when the patient perspires.

Treatment of Bed Sores.—Once bed sore has developed, its treatment differs from that of other peripheral ulcerations because, even though the area is infected, the application of disinfectant dressings usually aggravates rather than ameliorates conditions, since tissues deprived of nerve supply are easily attacked by chemical as well as bacterial agents. Since its introduction by Latimer, in 1934, the tannic acid-heat treatment of such ulcers has been widely and favorably used. Warm boric acid compresses are usually employed with results that are none too good; the continuous bath is preferable but its employment is not always feasible. When slough has separated or been curetted away and "stimulant" treatment seems indicated, the time-honored therapy is to use on alternate days the N.F. scarlet red ointment and a dressing of equal parts (more or less) of balsam of Peru and castor oil. The experience of Vorhaus *et al.* (1943) in a few cases indicated that the healing of bed sores might be promoted by the systemic administration of vitamin B complex. An amazing report has recently been made by Lamon and Alexander (1945) of the closure of several bed sores with the aid of penicillin given both parenterally and locally: the patient having received 100,000 units of penicillin intramuscularly for twenty-four hours, each of the wounds was carefully excised and the granulation tissue in the bed of the ulcers was removed *en masse* with the skin edges, 20 cc. of penicillin solution containing 250 units per cc. were injected copiously into and around each wound, and the wounds were then closed in two layers with interrupted sutures of number 40 white cotton (with the exception of one ulcer in which it was necessary to use a slightly heavier grade of braided silk); except for the extrusion of four of the silk sutures there had been no breakdown of the wounds in the three months which had followed the closure at the time the report was made.

Care of the Bladder.—If there is paralysis of the bladder every effort should be made to prevent overdistention with consequent dribbling and great danger of maceration of the skin on the one hand and urinary tract infection on the other. But no catheterization, not even the first, should be made under any but the most absolutely aseptic conditions. Catherization at six-hour intervals

is the usual procedure, always hoping that automatic emptying of the bladder will be established before the inevitable infection has occurred. When such infection occurs its treatment is that described in Nontuberculous Urinary Tract Infections.

Care of the Bowel.—It is customary to give a daily enema, preferably of sodium bicarbonate instead of soapsuds, and to leave the patient on the bedpan for an hour afterward so that all of the slowly returned water may be caught. Some men give a cathartic such as aromatic fluid extract of cascara at night also, but it is possible that this makes the likelihood of abdominal distention somewhat greater; this latter disturbance may cause great annoyance and necessitate administration of 1 cc. of pituitrin hypodermically.

Combating Dehydration.—In many instances it would seem advisable to give one or more 1-liter infusions of dextrose-saline daily until the patient is able to swallow satisfactorily. For the promotion of comfort it is also important to maintain the mouth in a moist state; Freeman (1941) wrote of the use of a water bottle with a gauze wick leading down into the patient's mouth to deliver water sufficiently slowly so that the occasional reflex swallowing would take care of the situation.

Combating Muscular Spasms.—The exceedingly distressing sudden painful spasms of the paralyzed limbs which occur reflexly in some instances when the cord has been severely damaged require the use of large doses of sedatives; see Insomnia.

Massage and Faradization.—In recent years there has been a trend away from routine employment of massage in hemiplegia; it is also felt nowadays that electrical stimulation of the muscles with faradic current is not only useless from the standpoint of reestablishment of nervous pathways but is actually harmful in that it goads into further spasm muscles which are already spastic.

Exercise.—Practice has moved away from sole dependence on passive movements; indeed, Hobhouse (1936) probably expressed the consensus when he said that in hemiplegia the only passive movements necessary are full movements of joints to maintain mobility and ensure positions of the limbs which will not permit the formation of deformities. On the other hand, everything possible should be done to begin active movements from the very start, before the initial flaccidity has been replaced by spasm. Attempt must be made to stimulate the patient's utmost effort of will as early as possible. Even during the beginning period, when there is likely to be some psychic change, something can be accomplished by persistence; Hobhouse said "irritability in itself provides a stimulus for movement and it is less to be feared than apathy." Metcalf (1934) recorded that in the return of muscle activity after his own stroke there seemed to be a threshold of resistance which had to be overcome and that this threshold lessened in needed duration in successive trials on any one day and from day to day. Hemianesthesia may impede recovery but it does not seem to necessitate modification of treatment. Expecting a patient to be constantly making efforts to use a paralyzed arm when there is a sound one at his service is asking a great deal; sometimes transient immobilization of the sound one promotes formation of a habit of attempting to use the other. Right hemiplegia in right-handed individuals is said to be more likely to be accompanied by aphasia than is left-side involvement, but Hobhouse found the prospect of motor recovery decidedly better when the right side was affected.

ECLAMPSIA AND HYPEREMESIS GRAVIDARUM

ECLAMPSIA

Eclampsia is a disturbance of pregnancy characterized in the end by convulsions, coma and a high death rate, and nearly always recognizable some time during the last trimester by the appearance of one or all of a triad of prodromal signs: hypertension, albuminuria and edema. The conception that this is a "toxemia," or as more frequently stated, that it is one of the "toxemias of pregnancy," completely lacks support since no one has ever found the alleged toxin or produced more than presumptive evidence of its existence. The pathologic findings, though characteristic in kidney and liver, are not such as can be demonstrated in eclampsia alone. Many theories of etiology are current, some quite interesting, some hopelessly weak, all inconclusive. But certain gross facts are crystallizing in clinical consciousness. One is that there are definitely two stages in the malady—preeclampsia and eclampsia—which differ in degree only. Another is that the serious symptoms are those of water retention. And another that if this retention is recognized early enough, much can be done to prevent its progression to the point at which life is threatened. Fortunately no intricate or protracted laboratory studies are necessary, for the diagnosis can be simply arrived at. Headache of sudden onset, visual disturbances, eyeground abnormalities, diminished urinary output, patent edema, nervous irritability—these are helpful but often late manifestations; excessive increase in weight, rise in blood pressure, albuminuria are the cardinal signs to seek and heed. They may appear and disappear independently of one another, but the presence of any one of them is warrant for action. Women do not normally gain more than 20 to 25 pounds during pregnancy; average gain during the last sixteen weeks is 1 pound per week, twice this gain is excessive and suspicious, three times is alarming. A rise in blood pressure from the normal 120/80 or less, to 135/90, or more, is suggestive evidence not to be ignored. Albuminuria is definitely not a normal thing.

In the late stage of the attack itself, the patient falls over unconscious, and passes from a rigid spasm with opisthotonos, flexed arms, clenched fists, distorted features and dilated pupils into a clonic convulsion, during which the whole body twitches very violently, the tongue is protruded and often severely mutilated by the champing jaws, the eyes are bulging and bloodshot, the face is swollen and cyanosed, blood-tinged foam comes from the mouth, and the pulse is rapid and pounding. The chest is rigidly fixed. After from thirty seconds to one and one-half or two minutes, relaxation takes place and the patient may wake up very exhausted and bewildered; or in the most severe cases, she remains in coma between spasms and may be delirious.

THERAPY

There are many methods of treating eclampsia; some of them, like the famous Stroganoff and its modifications, consisting in little more than heavy narcotic drugging when the convulsions occur; others, like the Rotunda, and the approach upon the basis of a supposititious hypoglycemia, relying principally upon the free administration of fluids when the convulsions appear;

others using bizarre drugs in allegedly more or less "specific" roles; and some attempting to combine the most liked features of all the others, thus winning strangely the appellation "conservative." I shall not attempt to present any of these methods here for the reason that it seems to me advisable only to present the more rational one which attempts both to prevent and treat the disturbance by concentrating all attention on combating water retention. The foremost advocates and routinizers of this type of treatment are the group associated with Arnold at Temple University in Philadelphia; what follows is a condensation of their plan.

Treatment of the Potentially Abnormal.—This is the group of patients who are apparently well but who have a history of definite or probable kidney-impairing disease or of previous pregnancy complications possibly involving the kidneys, as well as all with evidences of latent organic disease, especially of the kidneys.

(*a*) Place on a fluid balance basis at earliest recognition of pregnancy: 30 to 40 ounces (900–1200 cc.) of fluid intake and output daily.

(*b*) Five small meals daily with no food or drink except at these three-hour intervals.

(*c*) The diet should be very low in salt and sweets, the former increasing retention and the latter increasing thirst. Since Strauss (1939) found hypoproteinemia often present in the last trimester of pregnancy, the protein allowance should also be higher than ordinarily taken, for hypoproteinemia is in itself conducive to water retention.

Treatment of the Moderately Preeclamptic.—Patients who have some undoubted, even though moderate, indications of approaching danger: overweight, slight or marked edema, hypertension of 30 to 50 points; subjective symptoms still absent or only mild or variable.

(*a*) Drastically restrict fluids, or withhold altogether if it seems advisable, until twenty-four-hour urine output is known; then chart accurately the intake and output daily, or at intervals of a few days, as the case warrants.

(*b*) Dehydrate more or less moderately with a few daily, or every other day, courses of magnesium sulfate by mouth: 1 or 2 ounces (30–60 cc.) of the saturated solution every hour or two until watery stools are produced.

(*c*) Meals and dietary ingredients as in (*b*) and (*c*) under Treatment of the Potentially Abnormal above, except for the withholding of fluids.

(*d*) When sufficient dehydration is accomplished, as indicated by reduction in weight and blood pressure, endeavor to maintain water balance as in the preceding potentially abnormal group.

Treatment of the Dangerously Preeclamptic.—Those in whom there is already the threat of convulsive seizures: scanty urine, overweight, edema, alarming hypertension (50–100 points), urinary pathology; subjective symptoms—headache, visual disturbances, mental dulness, "indigestion"—often, but still not invariably, present. The treatment here may necessarily include the following:

(*a*) If the subjective symptoms indicate great urgency, drain the spinal canal of 40 to 80 cc. of fluid, or, if this is impracticable, withdraw 20 to 30 ounces (600–900 cc.) of blood by venesection.

(*b*) If the case is less urgent, or after one of the above measures has been taken, give 50 cc. of 50 per cent dextrose solution at four- to six-hour intervals, alternating two or three times in the intervals with 20 cc. of 10 per cent magnesium sulfate solution.

(*c*) The above injections being designed to draw water out of the tissues into the blood stream, magnesium sulfate purging must be employed to get rid of the water through the bowel.

(*d*) If marked improvement is not seen in twelve to twenty-four hours repeat the spinal drainage, or repeat it in four to six hours if symptoms continue urgent. Withhold fluid until output from bowel and kidneys, and weight reduction, indicate effective dehydration.

(*e*) In most instances food and restricted fluid intake may be allowed after twenty-four hours if the patient *asks* for it, but often it is necessary to withhold both for thirty-six to forty-eight hours.

Treatment of the Convulsive Group.—Patients who, antepartum or postpartum, have reached the convulsive stage or in whom there are signs of impending death without convulsions:

(*a*) Treat as above in all particulars except that the spinal drainage should be repeated at three- to six-hour intervals, and that an opiate or a barbiturate may be given to facilitate the first one if absolutely necessary. The number of drainages will depend upon their effectiveness in stopping the convulsions, restoring consciousness and promoting mental clearing. Venesection is rarely necessary in addition. Keep the patient warm but seek to avoid the use of hot packs.

(*b*) Arnold says that though some mortality is inevitable in this group, one may expect to keep it within 5 per cent. As to emptying the uterus, he says that by this planned cerebral dehydration they are enabled to "relieve the patient's head rather than her uterus."

HYPEREMESIS GRAVIDARUM

(*Pernicious Vomiting of Pregnancy*)

Ordinary "morning sickness" occurs in about 50 per cent of pregnant women, but the severe form with which we are here concerned is rare. It usually begins between the third and sixth week and lasts several weeks to months; the course may be continuous or intermittent. The symptoms are loss of appetite, nausea, persistent vomiting, foul breath, emaciation, intolerable thirst, mental aberration, headache, delirium, ketonuria, coma and death. The pathologic findings in the urine and blood are apparently entirely the result of starvation, dehydration and the loss of chlorides through vomiting. Many patients recover spontaneously, either quickly or slowly, but a few go on to death; before this final event miscarriage usually occurs and the stomach suddenly becomes retentive of food. The more severe form of the polyneuritis of pregnancy has generally been associated with hyperemesis gravidarum.

There is not as yet complete agreement regarding the cause of this malady, but the theory that it is due to a metabolic disturbance in the mother resulting in severe carbohydrate deficiency is at present serving very well as a point for therapeutic departure. Ideas regarding vitamin and endocrine deficiencies have gained some recent support. One observer is convinced that the trouble is due to the patient's allergic reaction to the secretion of her own corpus luteum; another has acted upon the assumption that there is hypersensitivity to all the tissues of the husband. The older classification of cases into neurotic, toxic and reflex types is no longer subscribed to by many observers.

THERAPY

Abortion.—Therapeutic abortion will cure all cases if the mother is not already too near death from starvation and exhaustion to stand the operation. But of course this is not advocated as a routine measure by anyone; indeed, when to empty the uterus is an obstetrical point of such nicety that its discussion has no place in a book of this sort. Certainly, under the newer treatment, this radical procedure is being resorted to much less frequently than was formerly the case.

Psychotherapy.—The nervous element must not be overlooked. Sometimes the severe symptoms will almost miraculously vanish when an obnoxious person, not infrequently the husband, is entirely banished from the presence of the patient; or she will suddenly recover when threats to employ the actual cautery or some other severe form of therapy are seriously made. A few observers believe that there is a psychopathic factor underlying all cases; Hurst, of England, has even gone so far as to say that the artificial termination of pregnancy cures merely by suggestion, since the patient naturally expects to recover when what she regards as the cause of her vomiting is taken away.

Carbohydrate Dietary.—The theory of carbohydrate deficiency or glycogen deficiency of the liver as the etiologic factor in the nausea and vomiting of pregnancy was extensively developed independently by Titus and Harding and their associates some years ago. The patient is placed on a regimen of at least seven small meals daily, beginning before arising in the morning and ending at bedtime. Carbohydrate foods of all kinds should be chosen, specifying particularly such articles as cooked fruits, dates and raisins, green vegetables, crackers and cookies, honey, sugar, and such desserts as puddings, custards and ices. In addition, Titus recommended the use of a formula as follows: $1\frac{1}{2}$ ounces of lactose and $2\frac{1}{2}$ teaspoonfuls of sodium bicarbonate dissolved in 1 pint of water, this being approximately 10 per cent of lactose and 2 per cent of soda in solution. Two ounces of this is to be taken every two hours.

Dextrose and Saline Intravenously.—In severe cases the patient is hospitalized if possible and given sedatives by rectum (such as 10 to 15 grains of chloral plus 30 to 45 grains of bromide in 100 cc. of water, night and morning, following a cleansing enema) and dextrose intravenously. The method of giving the latter varies—Titus: two or three daily infusions of 25 per cent solution, 75 Gm. of dextrose for the initial dose, 50 Gm. for the subsequent ones; Dieckmann and Crossen: 1000 cc. of 10 per cent solution three times daily; Kassebohm and Schreiber: 1000 cc. of 5 per cent every six hours; Hendon employed venoclysis, the continuous administration of 5 to 10 per cent solution for as many days as necessary. It is the consensus that insulin administration is not necessary as there is no evidence that this hormone is lacking; however, some men still "cover" the dextrose by giving 1 unit of insulin for each 2 Gm. of sugar. Of course if this is done one cannot look upon disappearance of ketonuria as evidence of improvement. Kassebohm and Schreiber (1937) laid down the dictum that response to therapy, if it is to be seen, will occur in forty-eight hours, the chief indications of it being diuresis, slowing of the pulse rate, elevation of blood pressure and complaint of hunger. The point should not be overlooked that the low blood chlorides need to be replenished; many men give the dextrose in saline solution.

Duodenal Tube Feeding.—Van Wyck believed that those who respond

slowly or not at all to the intravenous administration of dextrose show a persistent urobilinuria (in the absence of adequate laboratory facilities, urobilinuria may be assumed to be present when the urine has a characteristic orange-red color). This he interpreted as evidence of a gravely disordered liver function which calls for the administration through the duodenal tube of additional calories. The method is to give 3 ounces (90 cc.) of skimmed milk and the same quantity of 10 per cent dextrose solution every two hours throughout the twenty-four; this gives the patient 780 additional calories as well as 2000 cc. more water (see also below).

Vitamin Therapy.—Luikart (1933) believed that the exclusive employment of dextrose and large amounts of fluid may wash out considerable vitamin B complex, which may indeed have been lowered by the pregnancy itself. In the years since a number of men have stated their belief that supplementary vitamin therapy is advisable. Of the components of the vitamin B complex, pyridoxine (B_6) and thiamine (B_1) have the best records. Of the 10 patients of Weinstein *et al.* (1944), 8 obtained complete relief with the combined use of pyridoxine hydrochloride orally and intramuscularly, 80 mg. divided between four oral doses and one intramuscular injection of 100 mg. daily; in the other two patients other types of therapy had to be employed in conjunction. This report also included 68 patients who obtained marked relief from 10 to 20 mg. of pyridoxine three or four times daily in nausea and vomiting of less severe grade. Hart *et al.* (1944) found thiamine hydrochloride and pyridoxine hydrochloride combined in doses of 100 mg. each superior to pyridoxine alone or to doses of 50 mg. each of the two combined; the medication was usually given intravenously, repetition of the dose being usually futile if benefit was not obtained from the first injection; the results in primigravidas were much better than in multigravidas. Lund and Kimble (1943) concluded that vitamin C deficiency may be one of several serious consequences of hyperemesis gravidarum but does not in itself play a part in the cause of the disease; however, it might perhaps be the part of wisdom in all severe cases to administer ascorbic acid parenterally and as soon as progress permits add large amounts of vitamins A and D by mouth.

Adrenal Cortex.—This is one of the newer things in the treatment of a condition whose etiology is unknown. Freeman *et al.* (1937) reported excellent results in 16 cases in which the combination of dextrose and vitamin forcing was supplemented by the use of adrenal cortex. Kotz and Kaufman (1940), using the more refined and concentrated product now available, treated 50 cases, the dosage being 1 capsule three times daily before meals, sometimes supplemented by a daily subcutaneous injection of 1 cc. The latter observers found it difficult to evaluate the therapeutic effects of the agent but thought that most of the patients were markedly benefited. Hart *et al.* (1944) gave 2 cc. of adrenal cortex extract for a few days to 5 patients in whom vitamin treatment had failed; 3 of the patients were able to retain food when so treated.

Progestin.—Finch (1940) used injections of progestin (natural), the corpus luteum hormone, in attempting to "desensitize" 51 patients; he said 91 per cent of the series were relieved of symptoms. Dosage began usually with $\frac{1}{2}$ international unit of progestin in oil intramuscularly, 1 unit being given one day later; treatment then followed at forty-eight to seventy-two-hour intervals until vomiting ceased, increasing the dose gradually to 3 or 4 units if necessary; when vomiting ceased the top dosage was somewhat reduced and given at five- to seven-day intervals two or three times more. Vomiting was

said to have stopped in an average of about five days and nausea in eight days, the longest persistence of these two symptoms being nine and nineteen days respectively.

Husband's Blood.—The patient of Hughes and Martin always awakened after intercourse with a headache similar to that which she experienced eating certain foods to which she was sensitive; when she developed hyperemesis gravidarum it was felt that possibly the developing tissues of the fetus following the husband's characteristics also might be incompatible with the mother and that the severe hyperemesis was a response to this tissue incompatibility. Intramuscular injections of the husband's blood were therefore given in the hope that they would stimulate the formation of products that would counteract this tissue sensitivity. The patient had been pregnant on seven preceding occasions, having experienced severe vomiting and spontaneous miscarriage each time, but during the eighth pregnancy, with which the report was concerned, injections of the husband's blood were begun about the fourth week when nausea began. Thereafter $2\frac{1}{2}$ to $3\frac{1}{2}$ cc. of the husband's blood was injected intramuscularly every three to eight days throughout the entire pregnancy, the longest interval being two weeks. Great relief was afforded by these injections and the pregnancy went through uneventfully until the 36th week when it was thought advisable to induce labor because of threatened toxemia. Upon one occasion the patient's own blood had been substituted for that of the husband without effect. This is only one case report which may mean nothing, but it is certainly bizarre and interesting.

Nitrites.—Because of the alleged close relationship between pregnancy and the origin of biliary disease and because spasm of the second portion of the duodenum produced by morphine was accompanied in some cases by nausea or biliary colic, McGowan *et al.* (1938) studied the duodenum in 2 patients suffering from hyperemesis gravidarum. In each case spasm of the second portion was found and readily relaxed by inhalation of amyl nitrite. At the time of writing they had successfully treated 12 cases by the use of nitroglycerin; the patient is instructed to lie down for a little while after each meal, during which time she allows a hypodermic tablet of 1/100 grain (0.0006 Gm.) to dissolve under the tongue.

GENITO-URINARY INFECTIONS AND STONE

GONORRHEA

Gonorrhea in adults is contracted during the act of sexual intercourse and in the male appears primarily as an infection of the anterior portion of the urethra, the early involvement of the urethral glands, however, playing an important part in maintaining the infection. The average incubation period is three to five days. Profuse purulent discharge is the rule and is usually accompanied by painful micturition. Edema of the parts is not often sufficient to prevent free voiding, but infiltration of the corpus spongiosum is sometimes sufficient in degree to destroy the elasticity of the urethra so that on erection the penis curves downward, giving rise to the very painful symptom known as chordee. When the infection spreads behind the sphincter, which occurs in the majority of cases between the second and fourth weeks, the so-called "posterior" urethritis is established; in its train often come prostatitis, epididymitis and seminal vesiculitis. Gonorrhea in women is usually indicated subjectively in the beginning by a feeling of unusual dryness and discomfort about the genitalia; this is soon followed by a burning sensation and the appearance of a discharge, which is accompanied by smarting on urination and increasing in frequency. The infection is limited in its distribution, for it is only in the very young and the very old, when the cornified layer of epithelium has not yet formed or has disappeared, that the vagina itself is involved early. The primary points of localization are in the urethra, the urethral (Skene's) glands, the vulvovaginal (Bartholin's) glands and the endocervix. The vaginal walls and the structures around the vaginal orifice become hot and rough and tender but they are not in themselves infected by the gonococcus in the beginning. The discomfort of acute gonorrhea in women usually passes away very quickly, but the process nearly always becomes chronic, just as in the male. The natural barriers against the upward extension of the infection into the uterus and the adnexa are very great, but once this extension takes place the resultant endometritis, salpingitis, and so on, are serious affairs indeed. Noeggerath, in 1872, was probably the first to lay stress upon the importance of latent gonorrhea in the female.

Gonorrhea is believed to outrank in incidence a number of the common infectious diseases in children, but its true incidence is unknown. Its greatest frequency is in girls up to the age of five years, but it may occur at any age up to puberty. The disease is contracted indirectly from infected adults, through such media as clothing, bedclothing, towels, diapers, baths, sponges and innumerable other household materials. Perhaps in exceedingly rare instances the common toilet seat is the disseminator; most frequently, however, the disease is passed from child to child during precocious manipulation of the genitals. Rape is an infrequent cause. Some observers believe the cervix to be so frequently involved that the disease would more aptly be styled "cervicovaginitis." The symptoms are painful urination and pain on walking, pronounced redness and edema of the external genitalia, coapted labia majora and a thin watery secretion which soon develops into a thick, yellow, offensive discharge. The gonococcus can be demonstrated in about 50 per cent of cases;

rectal cultures are also often positive but clinical proctitis seems to be very rare. In the majority of instances the condition undergoes spontaneous cure in about three months (Cohn *et al.*, 1940), but in many children the infection causes considerable discomfort and lasts as long as six months, occasionally for several years. The impression that the disease terminates invariably at puberty is a common one, but Benson and Steer (1937) recorded 2 girls in their clinic still showing positive smears though menstruating six and eight months respectively at the time of report. Complications are fortunately very rare in these cases in childhood, though Maguire (1944) stated the belief that gonorrheal pelvic inflammatory disease occurs sufficiently often in young children to be considered in the differential diagnosis of acute abdominal pain in these patients.

Gonorrheal arthritis, first clearly described by Brande in 1854, and endocarditis are serious complications, which occur of course only after the organism has entered the blood stream in considerable numbers. If the gonococcus is conveyed to the conjunctiva by the hands or other contaminated object an acute infection often resulting in blindness follows; that this catastrophe does not occur with greater frequency than is the case is solely due to the fortunate fact that the organism perishes very quickly outside the body, though cases of its survival on damp towels for twenty-four and dry towels for twelve hours are on record (Dobszay, 1933). In most cases of gonorrhea there are few systemic symptoms beyond malaise and a slight headache, though the leukocytosis is indicative of a general reaction. Psychic disturbances are often quite pronounced, but they are probably for the most part engendered by the patient's fear that what he looks upon as his moral dereliction will be discovered.

Gonorrhea would seem to be as old as man, for very many of the ancient writings that have come down to us, both religious and secular, contain references to this "flow of semen" disease. However, so far as we now know, the true nature of the discharge and the recognition of the infectious and venereal nature of the malady were not recorded until quite late in the Middle Ages. Frenel, in the sixteenth century, seems to have differentiated gonorrhea and syphilis; apparently the disease was very common at that time, but in John Hunter's day (1728–1793) we find the two diseases again confused; Ricord, in 1838, finally established the separate entities. In 1879, Neisser discovered the causative organism, now known as *Neisseria gonorrheae*. Regarding the present incidence of the disease, it can only be said that it is very prevalent all over the world, but whether it is on the increase or decrease cannot be stated with any positiveness, though the draftee rejections in War II as compared with War I indicated that the incidence has declined in the United States.

THERAPY

Penicillin.—The introduction of the sulfonamides completely revolutionized the treatment of gonorrhea, but since it is now evident that penicillin is rapidly superseding these agents as the drug of choice I shall discuss the methods of employing penicillin first.

Long Course.—The term "long" is employed here to indicate the method of using penicillin in which treatment is extended beyond the period of a usual working day, *i.e.*, intramuscular injections are given every three hours for five or more times. Within two or three hours after the initiation of this type of penicillin treatment the urethral exudate undergoes a striking change, becoming paler, less viscous and much reduced in quantity. By the fifth or

sixth hour it has practically disappeared and stripping of the urethra usually produces only a small drop of clear watery secretion; the following morning there is usually no discharge and none can be produced by stripping the urethra. Tenderness, pain on urination and whatever subjective symptoms there may have been also disappear rapidly. Complicating epididymitis has usually much subsided within twenty-four hours and the swelling altogether disappears within a week. Long (1945) reported that in the treatment of 100 consecutive cases the smears were negative in four hours in 95 instances and in eight hours in the remaining 5 cases; in 35 cases the cultures were negative in four hours, in 91 cases in eight hours, and in all cases in twenty-four hours after the first injection. In a cleverly conceived clinical experiment, Miller *et al.* (1944) clearly showed that all of the effects of penicillin are due to its systemic action and not to any action exerted by it in the urine. The compilation of treatment results reported by Schwartz and Edge (1944), from the Division of Preventive Medicine of the United States Navy, was as follows: (*a*) of 4439 cases of sulfa-resistant gonorrhea treated with penicillin, 95.9 per cent were recorded as successes on the first course of therapy; (*b*) 40 of the 181 cases reported as failures on the original treatment were for some reason not retreated, but of the remaining 139 all but 2 were retreated successfully. Reporting a comparable United States Army study on 1686 patients, Sternberg and Turner (1944) wrote that one course of treatment with a dosage of 160,000 units per case effected cures in 98 per cent, 80,000 to 120,000 units in 96 per cent, and 50,000 units in 86 per cent. Of the 126 failures in this Army series, 85 were retreated with a 100,000 unit dosage and 91.8 per cent were cured; thus by retreatment of failures with a second course 99 per cent of cures were obtained. No case of penicillin resistance was encountered in the series and in later discussions Sternberg expressed himself skeptical that most cases of reported alleged resistance are really that. Penicillin therapy seems to be equally as effective in the gonorrhea of women as in that of men, as evidenced in many reports such as that of Greenblatt and Street (1944), of whose 109 female patients all but 5 were cured with one course and all 5 of the failures responded to the second course. Cohn *et al.* (1944) successfully treated 1 child five years of age with sulfonamide-resistant gonococcic vaginitis who became bacteriologically negative with a total dosage of 40,000 units of penicillin.

Short Course.—Van Slyke and Steinberg (1944) thought to effect cure by giving all of the injections within the period of an ordinary working day. Sixty-five patients were injected with 25,000 units intramuscularly at 9 A.M., 11:30 A.M., and 2 P.M., and with 50,000 units as a final treatment at 4:30 P.M., the total amount of penicillin administered being 125,000 units and the total time period seven and one-half hours. Their criteria of cure were that the post-treatment period continue for a minimum of eight days, that there be complete subsidence of all clinical evidence of the disease by the time of release, and that a minimum of three cultures be taken and all post-treatment cultures be negative. Many of their patients, who were seamen and anxious to get back to work, lapsed the post-treatment observation requirements, leaving them a group of only 43 for analysis; in these 43 patients satisfactory responses were obtained in 84 per cent. The authors felt that the true response was probably better than indicated by this figure since it was known that some of the men returned to the sex contact which had been the original source of the infection before the termination of the post-treatment observation period.

Single Injection.—Exley (1944) treated gonorrhea with a single injection of penicillin as follows: (*a*) 15 patients were given a single intramuscular injection of 50,000 units, there being 2 post-treatment relapses in the series; (*b*) 25 patients were given a single intramuscular injection of 80,000 units, there being 2 post-treatment relapses in this series; and (*c*) 15 patients were given a single intramuscular injection of 100,000 units, there being 1 post-treatment relapse in this series. Exley felt it undesirable and inexpedient to recommend one-day ambulatory treatment until further clinical studies have been made. Romansky and Rittman (1944) reported that a single intramuscular injection of penicillin (the number of units was not precisely stated) in a beeswax-peanut oil mixture had effected cure in 11 of 12 patients with gonorrhea, and Zinnamon and Seeberg (1945) confirmed them by curing 17 of 18 female patients with a single intramuscular injection of 150,000 units in a beeswax and sesame oil mixture. This type of single intramuscular injection would therefore seem to have a bright future. A comparison of the so-called penicillin X with ordinary penicillin, both used in a single injection of 25,000 units intramuscularly, was made by Welch *et al.* (1944). Sixty-four (94 per cent) of the 68 penicillin X-treated patients were cured and only 37 (64 per cent) of the 58 patients treated with the regular commercial penicillin were cured; so it seems that penicillin X will also bear watching.

The Masking of Syphilis.—Penicillin is curative in both gonorrhea and syphilis but in the latter disease a much larger dosage is required than in the former; hence there is great danger that in any case of penicillin-treated gonorrhea the early signs of syphilis may be masked and early diagnosis thus missed. The following abbreviation of a case report of Shafer and Zakon (1944) presents the possibility: on March 3 the patient was admitted to the sick list in the United States Navy with acute gonorrhea, the examining physician noting at the time a single papular lesion on the lateral side of the dorsal surface of the shaft of the penis. He was given 100,000 units of penicillin—five doses of 20,000 units at three-hour intervals—and on March 10 was returned to duty with a negative Kahn reaction and cured of the gonorrhea. Later, however, he noticed that the original penile lesion reappeared, and examination on May 3 revealed an atypical penile primary lesion, clinical evidences of secondary syphilis and strongly positive Wassermann and Kahn tests. Of this serious matter of the masking of syphilis through the penicillin treatment of gonorrhea, Canizares (1944) very well writes, it seems to me, that unless the amount of drug administered is increased to cope with both diseases in all cases, which is at present certainly impractical, the period of observation for syphilis of patients with gonorrhea treated by penicillin should be extended at least to one year and preferably much longer.

Sulfonamides.—Opinion regarding the efficacy of the sulfonamides in the treatment of gonorrhea has had to be radically revised in very recent times because it has become well known that a very considerable amount of sulfonamide resistance was found among patients in the armed forces during War II.

Course and Results in White Men.—Campbell and Carpenter (1944) gave the usual five-day course—15 grains (1.0 Gm.) of sulfathiazole four times daily for five days—to 804 hospitalized patients at Fort Bragg, North Carolina, hospitalization extending not to the point of confining the individuals to bed but merely to the wards in which they performed such duties as cleaning, sweeping, window washing and kitchen police. The patient was instructed to

wash the penis four times daily with tincture of green soap and water and to dry the parts thoroughly; to avoid traumatizing the penis by not stripping to see if a discharge was still present; to drink at least eight glasses of water daily in addition to the normal intake; and never to allow the bladder to become distended even at night. A cure was obtained from one such course of treatment in 65.2 per cent of the group. A second series of 134 white soldiers given the same five-day course of treatment while continuing their regular military duties and training was successfully treated in only 43.3 per cent of instances. In the Navy, Gorenberg and Shulman (1945) reported 64 per cent of successes in 131 white men who were hospitalized but only 26 per cent in 42 who were treated while on duty status. Campbell (1944), writing of the considerable experience obtained in the British forces in the Mediterranean campaign, stated that as the campaign progressed northwards up through Sicily and Italy considerably less than 50 per cent of acute cases of gonorrhea were found to respond to an initial course of sulfathiazole even though the dosage was considerably raised. Jacoby and Ollswang (1944) had their patients take 8 Gm. of sulfathiazole at one time with water in about two or three minutes in the presence of the physician; they felt that the results obtained in the series of 62 patients were as good as with the standard dosage method employing larger amounts of the drug over a longer period of time. The only other report of a somewhat comparable study I have seen is that of Strauss *et al.* (1944), who gave a total of 6 to 8 Gm. of sulfadiazine, half at 9 A.M. and the other half at 3 P.M., to a group of hospitalized patients, another group being given 8 Gm. of sulfathiazole in the same fashion. Again the results were about the same as those achieved by the most protracted methods, but the authors felt that this type of treatment should be used only in hospitalized patients when time is at a premium.

Course and Results in White Women.—Thomas *et al.* (1944) treated 355 white women according to one of two systems: (*a*) 1 Gm. of sulfathiazole four times daily for five days, or (*b*) 2 Gm. four times daily for two days and then 4 Gm. daily for three days. They obtained 60 per cent of cures after one such course of treatment.

Course in Vulvovaginitis.—In vulvovaginitis of infants and young girls Lewis (1941) employed the following plan of treatment in 89 cases: sulfathiazole in 4 divided doses at four-hour intervals for seven to ten days, the total dose per day not to exceed 30 grains (2 Gm.) and being based upon a calculation of $\frac{1}{2}$ grain (30 mg.) per pound body weight.

Results in Negroes.—It is clear from all reports that Negroes respond much better to the sulfonamides in gonorrhea than do whites, a fact as yet unexplained.

Criteria of Cure.—The new chemotherapy has outmoded the old provocative tests (failure of discharge to occur following indulgence in alcohol or sexual excitement, massaging over a sounded urethra, or the presence of gonococci in the discharge provoked by the injection of 1 per cent silver nitrate) as criteria of cure since patients will not respond to them after chemotherapy though smears and culture studies may still give positive results. New criteria of cure have therefore to be devised. Perhaps the most authoritative opinion in the matter is that voiced by a special committee for the study of this subject appointed by the American Neisserian Medical Society in 1943, who held that as scientific evidence of cure four consecutive negative cultures taken at intervals of two weeks, the first of these taken a week after apparent clinical

cure has been effected, may be accepted. In women one of these cultures should be taken immediately after menstruation. In the absence of cultural studies, the committee felt that all patients should be regarded as potentially infectious for a period of three months after symptoms disappear and that when having sexual intercourse during this period a condom should be used to protect the partner. Koch *et al.* (1944), following statistical analysis of treatment results in 926 cases in both males and females, stated that diligent search for gonococci over a period of three months will reveal their presence in 30 per cent of clinically asymptomatic sulfonamide-treated patients. Strauss and Grunstein (1943) were so convinced of the potential infectiousness of women during three months that, at the height of War II, they proposed the compulsory hospitalization of infected prostitutes for that period of time. Pelouze (1944) expressed himself to the effect that we are paving the way for a great epidemic of gonorrhea by dismissing the patient who is asymptomatic after a course or two of sulfonamides as "cured."

Causes of Failure of Treatment.—Some individuals who have failed to react favorably to the sulfonamides on the first course will do so very quickly on the second course, which is a fact not easy to understand. Schnitker and Lenhoff (1944) felt that the addition of urea to the regimen in the second course increased its efficacy somewhat; 30 Gm. of the urea were given daily by mouth for three days, 30 Gm. of the urea and the same sulfonamide in the same dosage on which the patient had failed previously for three days, then the sulfonamide alone for three days. Among the causes of failure to respond to two courses of therapy in the large series of Campbell and Carpenter (1944), above discussed, the chief was infection with a strain of gonococcus resistant to the drug; the second cause was a complication of gonorrhea in the genitourinary tract such as prostatitis, epididymitis, or periurethral abscess; the third cause was obstruction to a free flow of urine due to a small meatus, marked phimosis, or urethral stricture. Goodale and Schwab (1944), who developed a typing test for the accurate division of organisms into responsive and resistant groups, stated that in most cases sulfathiazole, sulfadiazine and sulfamerazine seemed to be equally effective (or ineffective) in gonorrhea both *in vitro* and *in vivo*. In borderline cases where differences in potency show up, sulfamerazine seemed to be definitely weaker and sulfadiazine very slightly weaker than sulfathiazole. Most clinicians of wide experience have found that in a few instances switching the patient from one to the other of these drugs will effect a cure, but the vast majority of resistant patients are in a class that does not respond to any of the sulfonamides. For these patients there are three measures to which one can turn: penicillin, heat therapy, or local treatment.

Combined Sulfonamide and Penicillin.—Oard *et al.* (1944) treated 232 patients as follows. On the first day 8 Gm. of sulfathiazole was given orally in four divided doses; on the second day 4 Gm. in divided doses was given concomitantly with the administration of 10,000 units of penicillin intramuscularly every three hours for five doses. The result supported the idea previously advanced by others that the sulfonamides enhance the effectiveness of penicillin since the proportion of cures was definitely greater than might have been expected from the use of only 50,000 units of penicillin alone. However, since all the patients in this series who were not cured by the combined use of sulfonamide and penicillin were immediately successfully treated with 100,000 units of penicillin alone, it is difficult to see what the practical advantages of

the combined treatment may be, except of course the economical one so long as penicillin remains expensive.

Heat Therapy.—Experience in recent years has amply shown that general hyperthermia therapy has a highly selective action upon the gonococcus and that many sulfonamide-resistant cases can be cured by resort to this measure. However, since penicillin has become freely available, it is doubtful whether resort will often be had to fever therapy in the future, especially as it is a difficult and somewhat dangerous procedure best carried out in well equipped centers by specially trained personnel. In the article on Syphilis there is a description of such measures as may be employed in general practice under special circumstances.

Local Treatment in the Male.—It is now the almost universally held opinion (Pelouze, 1944, to the contrary notwithstanding!) that nothing is gained by local treatment combined with the use of penicillin or a sulfonamide. The American Neisserian Medical Society took the position, in 1943, that local treatment should be employed only in cases resistant to chemotherapy. The directions of this group for the application of local treatment in these cases are abstracted here:

When infection is confined to the anterior urethra, give an anterior urethral injection once daily of not more than 6 cc. of 5 per cent mild protein silver or 0.5 per cent strong protein silver. The solution should be retained in the anterior urethra for only five minutes; its prolonged or too frequent use tends to perpetuate urethral discharge, an effect which may be recognized by the finding of many epithelial cells in the stained smear. All local treatment should be stopped if acute symptoms of posterior urethritis, such as urgency, painful or marked frequency of urination, or perineal or rectal pain develop. Treatment at this time must be limited solely to hot sitz baths, and when acute symptoms have subsided, anterior urethral injections are to be resumed and continued until prostatic stroking (massage) is begun.

Extremely gentle prostatic stroking (massage) should be tried when the second glass of urine has been clear, and the first glass nearly so, for two weeks. If this massage is painful or causes a recrudescence of other symptoms it should not be repeated for one week or until the symptoms have subsided. If it is not painful and if no recrudescence of symptoms occurs, the gland should be gently stroked at three- or four-day intervals, the smears and prostatic secretion examined every two weeks. *When prostatic massage is instituted too soon or applied too vigorously it often induces complications and retards the cure.*

No instruments of any type should be passed into the urethra while gonococci are present.

Local Treatment of the Female.—Local treatment has been shown to be unnecessary and not helpful during the treatment with penicillin or a sulfonamide. The local measures which are indicated in a small portion of patients who do not respond to chemotherapy are gynecologic matters whose discussion has no place in a book of this nature.

Local Treatment in Vulvovaginitis.—None of the local treatments for this condition had ever been established upon a satisfactory basis; now they have all been superseded by the systemic employment of the sulfonamides or penicillin.

Estrogen Therapy in Vulvovaginitis.—This type of therapy has been superseded by the chemotherapeutic measures in the practice of most men, but Compton *et al.* (1945) stated the belief that the estrogens should still be

considered the drug of choice, reserving sulfonamides for more lethal diseases in which their use may become imperative; it is very doubtful, it seems to me, if this viewpoint will meet with general approval.

Complications in the Male.—It is now rarely indeed that complications occur in the case that is promptly treated with one of the chemotherapeutic agents. When such complications are present at the start and fail to yield to the drug it is mandatory to have specialist consultation or to refer the case—something should be left to the venereologists The minor matters of chordee and phimosis, still sometimes seen, usually respond to the soaking of the penis in hot water. Allison (1944) reported that the placing of the end of a rubber tube attached to a powder blower in the opening of the foreskin and the vigorous blowing of zinc peroxide powder about the glans penis and under the foreskin is a measure that is very helpful in effecting reduction of the swollen prepuce. Of the treatment of paraphimosis, Pelouze (1936) wrote: "The foreskin should be replaced as early as possible to prevent induration and ulceration at the point of greatest constriction. In order to do this the glans penis should be grasped by the gloved fingers of one hand, while the other hand is used to encircle the swollen, misplaced prepuce. Gentle, continuous pressure should be made upon both structures until about all of the swelling is gone. The parts then usually are easy to place in their normal positions. To prevent subsequent retraction it is well to pass a strip of adhesive plaster along one side of the penis, over part of the preputial opening in such a way as to make it smaller, but not occlude it, and then down along the other side of the penile shaft. This should be left on for several days. In the presence of neglected paraphimosis with much induration it occasionally is necessary to incise the constricting band on the dorsum of the penis. If ulceration has taken place it is wise to attempt to sterilize the surface by the application of tincture of iodine before incision of the constriction. Ulcerations of the glans penis from prolonged penile constriction usually heal promptly upon the use of an antiseptic dusting powder. Before this is used, however, a darkfield study of the ulcer fluid should be carried out."

Complications in the Female.—Such of these as do not yield to the chemotherapeutic agents are gynecologic affairs entirely outside the province of this book.

Chemotherapy of Ophthalmia Neonatorum.—The treatment of these cases with sulfonamides has greatly decreased the duration of the disease and practically eliminated complications. The drugs are given systemically and local therapy and mechanical protection of the unaffected eye are apparently considered unnecessary nowadays; the eyes are simply cleansed with cotton moist with physiologic saline solution, no attempt being made to force the eyes open or to irrigate. Blumberg and Gleich (1943) reported that the following was satisfactory in their series of babies: sulfathiazole by mouth in the form of an emulsion with acacia, 3 grains (0.2 Gm.) of the drug initially, followed by 1 grain (0.06 Gm.) every four hours until symptoms disappear and the smears from the conjunctival sac show no gram-negative diplococci.

Sievers *et al.* (1944) reported the successful employment of penicillin intramuscularly in 6 of 8 patients, the dosage varying from 60,000 to 330,000 units. Seelig (1945) reported the local employment of penicillin in a patient who was not responding to the systemic employment of both penicillin and a sulfonamide: 0.25 cc. (1250 units) of penicillin were injected into the right eye subconjunctivally along with 1 minim of 5 per cent procaine hydrochloride:

this was followed by direct instillation of 3 minims of a solution containing 500 units of penicillin into the conjunctival sac every half hour as a corneal bath, the subconjunctival injection being repeated every fourth day for twelve days and the corneal bath for fourteen days. The corneal ulcers were touched daily during the first seven days with 100 per cent trichloracetic acid and three times during the following ten days, dilatation of the pupil being maintained with atropine or scopolamine and heat being applied as often as was practicable. After twenty-nine days of active therapy the patient's visual acuity was 20/20 and the ulcers were completely healed with two small scars remaining at the periphery of the cornea.

SYPHILIS

(See under *Infectious Diseases*)

CHANCROID

Chancroid is, next to gonorrhea, probably the commonest of the venereal diseases in the male. It would seem that the organism is able to maintain a saprophytic existence in the female, for the ulcerations are comparatively rare in women, even in those who are known to have been the direct infecting source of men; however, they do occur, and O'Leary (1945) has reported an interesting case of chancroid of the uterus in a woman whose husband apparently transmitted the disease to her though at the time he did not himself exhibit any ulcerative lesions of the genitalia. The bacillus of Ducrey is the causative agent but is very difficult to find. Though the intradermal test of Ito-Reenstierna is nowadays available for use in doubtful cases, diagnosis is usually still made upon clinical findings, having always uppermost in mind the necessity to make thorough darkfield examination to eliminate the possibility of the lesion being syphilitic in origin. The incubation period is usually considered to be three to five days but occasionally it is as short as one day; in Satulsky's *et al.* (1945) series of 1555 cases it was three to ten days. The first sign of the disease is the development of one or more small ulcers with a dirty base; these usually spread rapidly, by contiguity and continuity, discharging more or less pus, bleeding freely and causing destruction of tissue. The most frequent site of the initial lesion is the coronary sulcus, but the process may begin at any point on the penis; extragenital lesions are extremely rare, but spread by auto-inoculation may take place on the surrounding pubic region or on the abdomen and thighs. Intra-urethral chancroid has been recorded. As the ulcerations spread, there is much pain and inflammation and swelling of the affected parts. In the individual with a long foreskin there often occur varying stages of phimosis and paraphimosis. In about 50 per cent of the cases, especially those remaining ambulatory, the draining lymph glands are affected, giving rise to the condition known as bubo.

John Hunter (1728–1793) clearly distinguished between true syphilitic chancre and this false, "soft" chancre. Ducrey discovered the causative *Hemophilus ducreyi* in 1889.

THERAPY

Sulfonamides.—Experience in recent years has shown the systemic employment of sulfonamides to be superior to local treatment in all stages of the infection—ulcer, bubo ruptured or bubo unruptured. The simple local treatment nowadays employed (see below) is of an entirely new sort. Sulfanilamide, sulfathiazole, or sulfadiazine is effective, but sulfathiazole seems still to be the preferred drug. In the treatment of 1555 cases, Satulsky (1945) gave sulfathiazole or sulfadiazine in a dosage of 15 grains (1 Gm.) four times a day for five days followed by 7½ grains (0.5 Gm.) four times a day for ten days; or sulfanilamide was used in dosage of 15 grains (1 Gm.) three times a day for five days followed by 10 grains (0.6 Gm.) four times a day for ten days. The average hospitalization of all lesions in this series was 11.2 days. In a smaller series of cases, only 73 patients being included, Greenwald (1943) started sulfathiazole therapy with an initial dose of 30 grains (2 Gm.) and under his regimen all patients rapidly improved with an average of 7.6 days of time lost from duty, no patient being discharged from the hospital until the lesions had become completely covered with epithelium. There were 6 recurrences in Greenwald's series but all responded well upon readmission; indeed 4 of them had received less than seven days' treatment in the first course, and one case listed as a recurrence was probably really a reinfection since there was a time lapse of ninety-two days between the first and second admissions.

There is no reason why sulfonamides should not be administered while the organic arsenicals are being used in the treatment of a concomitantly contracted or preexisting syphilis.

Penicillin.—This agent has not been effective in the treatment of chancroid. Indeed in Pereyra and Landy's (1944) study in patients experimentally inoculated, it seems that the intramuscular injection of penicillin actually facilitated the development of a chancroidal lesion. However, one exceptional case, which probably proves nothing, was reported by Day (1945), that of a woman who was switched to penicillin when she became violently ill under sulfathiazole and in whom cure seemed to have been effected by the penicillin in about ten days.

Local Treatment.—The accessible lesions are cleansed with soap and water, dried, and covered with sulfanilamide or sulfathiazole powder or sulfathiazole ointment. This treatment is repeated daily by those who employ it but as a matter of fact many men no longer find it of advantage to use the sulfonamide locally when it is being given systemically. The treatment of phimosis and paraphimosis is discussed in Gonorrhea.

Bubo.—Greenblatt (1943) stated authoritatively that the bubo should never be incised. If fluctuation is present the bubo may be aspirated with aseptic care, repeatedly if necessary, but incision is never to be made. The aspiration point should be dusted with sulfathiazole powder or a dressing of 5 per cent sulfathiazole cream may be applied. In his large series of cases, Satulsky (1945) introduced 1 to 1.5 cc. of 7 per cent tincture of iodine through the cannula after all of the pus had been aspirated from the cavity; moderate burning pain was caused by this treatment in some patients. Following removal of the cannula a pressure bandage was applied and the patient kept at bed rest for three or four days, during which time there was drainage of an iodine-stained semipurulent serum and clumps of purulent material; in five to seven days the area was completely healed without any sequelae.

BALANITIS

Erosive balanitis is an infectious venereal disease due to the symbiosis of a fusiform bacillus and a spirochete, both of which are anaerobic and structurally resemble those found in Vincent's angina. It is a fairly uncommon affection even in large venereal clinics. Red superficial lesions with a necrotic border appear on the glans or foreskin and enlarge peripherally and become confluent to form circinate lesions with polycyclic borders. They do not give rise to bubo, though there is sometimes an inguinal adenitis. The thin yellow abundant pus is very foul-smelling. Phimosis is an early and annoying complication. There are usually no constitutional symptoms, but in rare instances gangrenous extension suddenly begins to take place very rapidly, the glans and prepuce, and in some instances the entire shaft of the penis, being destroyed in a surprisingly short time. In this gangrenous form of the disease there are always grave constitutional symptoms and death is frequent.

THERAPY

The key to the treatment of this disease lies in the fact that the organism does not flourish when exposed to oxygen. The usual practice is to open the prepuce by a dorsal slit, so that the glans is completely uncovered, and then to keep the parts clean either by wet dressings or by continuous irrigation with 2 per cent solution of hydrogen peroxide. Most cases of the erosive type heal rapidly under this treatment, especially if the parts are kept exposed to air at all times when the oxidizing agent is not being used.

The use of neoarsphenamine intravenously, as in the treatment of syphilis, is said to hasten recovery. In cases of other genito-urinary lesions complicated by a superimposed fusospirillosis, Greenblatt and Wright (1936) obtained good results from applying liberally to the lesions once or twice daily, after preliminary thorough cleansing with sodium perborate solution, the following mixture: 6 Gm. neoarsphenamine, 30 cc. glycerin, 30 cc. cod liver oil.

Sutton has described the use of subcutaneous injections of oxygen in a case of the gangrenous type as follows: "When I first saw the patient, five days after the onset of the disease, almost the entire dorsum of the penis was involved, the skin and subcutaneous tissues being soft and gangrenous. During the following thirty-six hours the infection continued to spread, despite the frequent and liberal use of hydrogen peroxide, by irrigation and by moist packs. At this time subcutaneous injections of oxygen were begun, by means of an ordinary hypodermic needle connected to an oxygen tank through a small rubber tube, and repeated every four hours. The normal tissue surrounding the affected area was first treated, the flow of gas being regulated by means of a small screw clamp encircling the outlet tube. Afterward the involved structures also were thoroughly impregnated with the gas. Within six hours the progress of the disease was checked, and within twelve hours it was completely under control. Shortly afterward the slough began to separate, and recovery, aside from the deformity resulting from loss of tissue, was prompt and uneventful." Balanitis being an uncommonly encountered disease, it is not probable that this type of treatment has been much employed; indeed, I have neither seen nor heard mention of its use other than in this one case of Sutton's.

GRANULOMA INGUINALE

(Granuloma Venereum)

Granuloma inguinale is a chronic infectious, ulcerative process, usually involving the genitalia or neighboring parts, and showing no tendency toward spontaneous healing. Most of the cases are seen in young adults with perhaps an even distribution between the sexes. Here in the United States it is predominantly a disease of Negroes, and in India the preponderance of Hindu over Mohammedan cases is said to be very high; I do not know to what extent the matter of racial preference has been investigated in other parts of the world. Granuloma inguinale is probably not venereal since wives or husbands often are not affected though continuing to cohabit when one is infected. The process begins as a small moist papule which rapidly ulcerates; thereafter, invasion of the surrounding tissues by the elevated, reddish, often shiny, delicately skinned granulomatous proliferations is gradual and eccentric. Where moist, the lesions are superficially ulcerated, but where dry they are cracked. Adenopathy is characteristically absent except in rarest instances, though the occurrence of elephantiasis of the genitalia, or of a leg, signifies involvement of the lymph channels. Except for the presence of the lesions and a slight itching or burning sensation, the patients experience little discomfort. The discharge from the ulcerating areas is held by some observers to have a quite characteristic odor, but having once seen the entire staff of a reputable hospital led temporarily away from their correct clinical diagnosis of epithelioma by the asseveration of an expert in this disease that he "smelled granuloma in the ward," I am extremely doubtful of the value of this diagnostic sign. Anderson *et al.* (1945) are attempting to standardize a diagnostic skin test employing antigens obtained from the organism which they have described (see below). Wilson's (1930) study of a small series indicated rapid progression and a tendency toward stillbirth in cases complicating pregnancy. Arnell and Potekin (1940) stated that 38 cases of granuloma inguinale of the cervix had been observed at Charity Hospital in New Orleans in the ten years preceding their report; Crane and Kimball (1940) described a case in which there was involvement of the rectum and colon; in Becker's (1939) case autopsy showed involvement of the intestinal tract and the ribs; in the three cases of Lyford *et al.* (1944) there was associated polyarticular arthritis and osteomyelitis; and in the case of Paggi and Hull (1944) there were many metastatic lesions in the bones and very severe constitutional symptoms. Extragenital skin lesions have been occasionally reported.

The disease was recognized by MacLeod, in India, in 1882, but it was first accurately described by Conyers and Daniels, in British Guiana, in 1896. In 1905, Donovan, in India, first described the organism now believed to be causative, but strange to say it is not definitely known as yet whether this organism is a protozoan or a true bacterium, though Anderson *et al.* (1945) have very recently reported the cultivation in embryonic yolk of an organism which they believe to be a bacterium and to be the true causative agent. The organism is found in all parts of the lesions, but especially in the deeper areas, where all other organisms are absent. The characteristic histologic picture described by Pund and Greenblatt in 1937 now seems to be recognized by other workers as well; Alexander and Schoch (1940) found the use of Giemsa stain necessary to bring out the pathognomonic giant-cell. Increasing knowl-

edge indicates that the disease is practically world-wide in its distribution; here in the United States it is undoubtedly more prevalent in the South than elsewhere.

THERAPY

Antimony has had a long trial but its record is certainly not brilliant; the newer compounds are considered to be less toxic than tartar emetic itself. Antimony toxicity is discussed in Kala-Azar.

Tartar Emetic.—Antimony and potassium tartrate was first used in the treatment of this disease by Aragão and Vianna of Brazil. In cases which respond satisfactorily the lesions involute progressively and the Donovan bodies disappear. It is usual to use a 1 per cent solution beginning with 2 cc. intravenously and increasing 1 to 2 cc. at a time until 10 to 12 cc. are being given at a dose. The injections are given at intervals of two to three days. Ten or 12 injections may clear the lesions sufficiently that it is difficult to hold the patient for further treatment, but to avoid relapse weekly injections should be given for two or three months after entire healing, followed by 2 injections monthly for four months. According to Robinson *et al.* (1942) only freshly prepared solutions should be used, the stock solutions in ampules being found by them of little value. It is now the consensus that good results are to be expected only in early cases; Greenblatt (1943) said that cure may be obtained in practically every case when the diagnosis is made within the first six months of the infection, that over 50 per cent of patients with lesions of several years' duration will respond much more slowly and with frequent recurrences, and that in neglected or therapy-resistant patients the lesions will gradually become very extensive and the patient will become bed-ridden and cachectic and will finally die of the disease. Response to the drug seems to be much less complete when syphilis is present as a complication.

Antimony Sodium Thioglycollate.—The dose of antimony sodium thioglycollate is 0.05 to 0.1 Gm. dissolved in 10 to 20 cc. of sterile water and given intravenously every third or fourth day until 15 to 25 injections have been given. This drug was introduced a great many years ago but it does not seem to have been much employed; however, Robinson *et al.* (1942) reported its use in two patients who did not respond to tartar emetic and that in them the lesions healed promptly with 6 to 8 doses respectively.

Fuadin.—Williamson (1933) and his associates reported enthusiastically upon their success with this trivalent compound of antimony and sodium in 14 cases. Their treatment consisted of 12 intramuscular injections on alternate days of a 7 per cent solution; the first injection was of 1.5 cc., the second of 3.5 cc., and the subsequent injections each of 5 cc. More recently, Arnell and Potekin (1940) said they found tartar emetic the better drug; Goldblatt (1939) thought the results with both fuadin and tartar emetic "rather disappointing"; and Greenblatt (1943) said that fuadin was superior to tartar emetic and more convenient to administer.

Antimony Thioglycollamide.—Hazen *et al.* (1932) used this agent with "striking therapeutic response" in 3 cases; Senear and Cornbleet (1932), and Patch and Blew (1930), also used the drug successfully. I have seen no recent reports of its performance though it continues to be Council-accepted.

Anthiomaline (Lithium antimony thiomalate).—This is the newest of the compounds. Greenblatt (1943) seemed to consider its usefulness about the

same as that of fuadin. Robinson *et al.* (1942) used it as the sole drug in four cases and obtained cures in all; in 9 tartar emetic-resistant cases satisfactory results were obtained in only 2.

Penicillin.—Nelson (1944) reported the treatment of two patients with penicillin; no beneficial effects were observed.

Podophyllin and Scarlet Red.—Tomskey *et al.* (1942) reported rapid healing when podophyllin was used locally while tartar emetic was being used systemically in 20 patients; it was said that the period of hospitalization was much reduced and the extent of the healing much more complete than under any other type of treatment. The following is the regimen of local treatment: (*a*) eliminate secondary infection by cleansing the lesions with hydrogen peroxide and giving hot sitz baths twice daily; (*b*) apply 20 per cent podophyllin in olive oil to the lesions after each bath, applying a local anesthetic such as pontocaine, metycaine or nupercaine ointment, ten minutes before the podophyllin application to prevent the pain of which many patients complain; (*c*) discontinue podophyllin application when the exuberant granulations have disappeared and a healthy base is evident and then apply scarlet red ointment after each bath in order to stimulate epithelialization; (*d*) when necessary continue to apply podophyllin to small resistant areas around the edges while the rest of the lesion is apparently healing.

Surgery and X-Ray.—Surgical excision of the lesions is referred to by a number of writers, but the most specific recent reference I find is that of Robinson *et al.* (1942). They employed surgical excision in 16 cases, in 14 of which other measures had failed; complete healing followed the operation in 9 instances and partial healing in 5. Greenblatt (1943) said that if lesions are extensive several courses of radiation therapy should be administered in dosage similar to that employed in the treatment of skin cancer; but in the three cases of Robinson *et al.* (1942) such therapy did not bring about involution of the process in any instance.

LYMPHOGRANULOMA VENEREUM

(*Lymphogranuloma Inguinale, Climatic Bubo, Venereal Lymphogranuloma, Lymphopathia Venereum*)

This is a specific venereal disease which always follows sexual exposure and therefore is seen with extreme rarity in children. Men predominate among the victims of the inguinal form, but the anorectal localization is seen often enough in women (occasionally in men also) probably to equalize the sex distribution; elephantiasis of the pudenda is also a manifestation of this disease. The initial small lesion on the external genitalia is not often seen, but it is known that the incubation period after exposure is between three days and three weeks. Usually the glands of only one side are involved but bilateral cases are on record; there is gradual progression until a first-size mass bound together by periadenitis is formed, and then breakdown and fistula formation take place; a thin seropurulent fluid drains for weeks and months. Occasionally, however, no breakdown occurs. The rectal cases usually lead to serious stricture interfering with defecation, complicated with infection of the rectum, anus and perirectal

tissues; the most dreaded complication is rectovaginal fistula. The studies of Wilson and Hesseltine (1942) and Finn (1944) indicated the possible hazard of mismanaged labor if the pelvis is obstructed. Constitutional symptoms of varying severity are observed in the majority of cases in the acute stage. Remote lesions suggesting a generalized systemic infection have been described—recent records include Zarafonetis' (1944) report of two cases of meningoencephalitis—but in their authoritative review D'Aunoy and von Haam (1939) took the position that in view of the rarity of remote lesions and the frequency of localized genital lesions it may be assumed that in most instances disseminated virus is soon destroyed. That the causative organism is a filtrable virus was shown by Hellerström and Wassén, in 1913; it is transmissible to several laboratory animals, but the several reports of its successful cultivation have not as yet been universally accepted. The antigen diagnostic test introduced by Frei in 1925 has greatly stimulated the study of this disease; it is now recognized, however, that the test is positive in some instances in which there are no clinical evidences of infection. Perhaps the complement fixation test of Grace and Rake (1943) will prove both more sensitive and easier to employ.

It is now thought that John Hunter treated cases of lymphogranuloma inguinale because of some descriptions in his "Treatise on Venereal Diseases," published in 1786; many men later described similar clinical pictures, but the individuality of the disease and its probable venereal nature were only truly pointed out by Durand, Nicholas and Favre, in 1913. Originally considered to be only tropical in its distribution, it is now recognized as occurring practically everywhere, though the greatest incidence seems to be in the warm, humid lands; however, Schutte and Lubitz (1940) found 33 cases in the proctologic clinic of our own school here in Milwaukee.

THERAPY

As in the therapeutic approach to all relatively "new" diseases, a host of remedial agents has been tried: quinine, organic arsenicals, antimonials, sulfonamides, diathermy, local application of a filtrate from infected glands, Frei antigen injections, autoserum, x-ray, radium, foreign protein and other fever therapy, surgical extirpation of the glands. Description of the methods of employment of only a few of these seems worth while at the present time.

Sulfonamide.—There have been numerous reports of the satisfactory use of the sulfonamides, particularly in the early stages; but taking into account the tendency to spontaneous recovery in this disease, some of the results have not seemed to me particularly brilliant. However, Grace (1943), who has had plenty of experience, categorically stated it as well established fact that sulfathiazole will cause the regression of the adenitis, suppurative and nonsuppuraative, within a period of approximately five weeks. He said the drug should be administered in a course of 22½ grains (1.5 Gm.) three times daily for two weeks, followed immediately by 15 grains (1 Gm.) three times daily for three weeks. The manifestation of the anorectal disease which is most responsive to sulfonamide therapy—still according to Grace—is proctitis, which, unlike lymphogranulomatous adenitis, seldom heals spontaneously. Cases of short duration without stricture can be completely healed, but long-standing cases and all with stricture, require at least one year's therapy with rest periods of from two to three weeks after each course of treatment. The amount of anal discharge is said to lessen shortly after treatment is begun and ultimately to cease. Grace said that in a number of instances in which anal discharge and

inflammation of the anorectal mucosa had reappeared after apparent cure, resumption of sulfathiazole therapy had again controlled the situation.

Antimonials.—In 1939 D'Aunoy and von Haam reported that their best success had been with antimonials. Recently anthiomaline (lithium antimony thiomalate) has had considerable trial. In the United States, Shaffer (1942) injected it intramuscularly in a dosage of 0.12 to 0.3 Gm. in aqueous solution, repeating injections two to three times a week in courses of 2 to 4 Gm., totaling 12 to 20 injections. It was his conclusion that the drug was not a completely satisfactory preparation for the treatment of all forms of the disease but that it appeared to be highly effective in cases of inguinal adenitis and that in the majority of instances of the anogenital syndrome it did at least cause a temporary arrest of the active symptoms. Shaffer's series comprised only 33 cases, but Law (1943) used anthiomaline in West Africa in 137 cases, though in a few instances he found it necessary to substitute tartar emetic when the newer drug was not available. He found that results were just as favorable with antimony as with sulfonamides.

Virus Injection.—Wien and Perlstein (1937) had some success with the use of Frei antigen in early cases; Howard and Strauss (1935) also cautiously mentioned their favorable impression in a small series of cases; 0.1 cc. of the antigen is injected intradermally biweekly until symptoms are alleviated, weekly thereafter. Kornblith (1939) gave the antigen intravenously in 207 cases, the injections of 0.3 cc. being given on alternate days three times weekly. In most instances the treatments were continued through many months, in some instances several years. It was said that the best results were obtained in the group with glandular involvement only, with symptomatic relief in some of the rectal and genital cases; but to me on the sidelines it seems difficult to place very much credence in these findings with treatment extended over such long periods and an acknowledged spontaneous healing in 33 per cent of cases without any treatment. It seems that each injection produces headache and malaise in about three quarters of the cases but that usually only the first two cause a severe systemic reaction with chill, fever, joint pains, skin rash, etc.; in a small proportion of instances the reaction is delayed for twenty-four hours and then is very severe and lasts several days.

Grace (1943) stated his belief that lymphogranulomatous proctitis should be treated by alternation of a sulfonamide compound and inactivated virus, the latter to be administered intravenously and derived from the infected chick embryo. It was his feeling that the failures in the injection of Frei antigen were due to the low concentration of virus in the human or mouse brain preparations employed, an objection which would not apply to the inactivated chick embryo virus, the use of which he advocated.

Autoserum.—Marks (1942) treated 50 patients by reinjection of their own serum. Ten to 15 cc. of blood were removed from the median basilic vein and the serum separated from this was injected under the skin of the abdominal wall. There were no severe local reactions and apparently no systemic ones. Treatments were given at four-day intervals in a course of twelve injections; then two weeks' rest between series and such treatment continued as long as improvement was evident. Marks considered that this method of therapy gave as good results as anything else he had tried.

NONTUBERCULOUS URINARY TRACT INFECTIONS

(*Cystitis, Pyelitis and Pyelonephritis*)

Therapy in these infections has been much altered by the introduction of the sulfonamides. Mandelic acid, methenamine (urotropin) and neoarsphenamine still have occasional indications, but there is no longer any need to clutter up the pages of the book with descriptions of the other drug technics.

Sulfonamides.—These drugs have certain very definite advantages over mandelic acid which I shall list as a means of emphasizing the properties of the sulfonamides themselves. *First:* They can be given in the acute stage of the infection which, especially in infancy, is a definite advance over the previous use of only diuresis and alkalization. *Second:* Their action is not dependent upon the reaction of the urine. This not only frees us from the necessity of insuring an acid urine by means often objectionable to the patient but also enables us to overcome *Proteus ammoniae* and a few other less frequently encountered organisms which through their conversion of urea into ammonia prevent acidification of the urine; indeed, Sickler (1940) showed that the activity of the sulfonamides is actually somewhat greater in alkaline than in acid urine. *Third:* When renal function is subnormal administration of mandelic acid is not only injurious but useless—injurious because itself a renal irritant it also promotes acidosis by reason of the inability of the injured kidney to excrete it; and useless because the damaged kidney is unable to produce an acid urine in which the mandelic acid can exert its antiseptic action. These conditions do not apply to limit the activity of the sulfonamides for they appear in the urine in effective concentration even though the blood urea is well above normal. *Fourth:* These drugs are apparently able very often to clear up infection in which there is an associated chronic prostatitis due to the fact that they appear in the prostatic secretion; in instances, however, in which nonspecific prostatitis is found in the routine search for foci of infection, without urinary tract infection being symptomatically recognizable, these drugs have been of little or no value.

The studies of a number of workers, but principally Helmholz (1941), showed that sulfathiazole was superior as a urinary antiseptic to the earlier members of the series. Greene *et al.* (1942) found the newer drug sulfadiazine slightly less effective than sulfathiazole, and more expensive but less toxic. However, La Towsky (1943), in a study involving 100 patients, obtained results with sulfadiazine that he thought nearly equivalent to those obtainable with sulfathiazole and felt that the smaller incidence of toxicity and the less severe toxic reactions with the newer drug should cause it to be favored. Alyea and Parrish (1943), in a study involving 152 patients with uncomplicated urinary tract infections, found both sulfadiazine and sulfacetamide superior to their predecessors among the sulfonamides. Several other observers have also reported favorably upon sulfacetamide. So what it all seems to amount to is that we have at least three sulfonamide agents of superior value for employment in urinary tract infections: sulfathiazole, sulfadiazine and sulfacetamide. Everett *et al.* (1945) have made the interesting observation that sulfasuxidine is quite effective in the treatment of infections due to *E. coli* despite the fact that it does not reach a sufficiently high titer in the blood and urine to make it an effective agent there; the reasoning of this group of observers in explanation of their findings was that when sulfasuxidine is used the tissues of the urinary tract are given an opportunity to rid themselves of the existing infec-

tion because the constant source of this infection in the bowel is temporarily eliminated. The advantage of having more than one agent was well developed in some of Alyea and Parrish's cases; for example, one patient who had a mixed infection of coccus and bacillus became asymptomatic on sulfacetamide, the bacilli disappeared, but the cocci persisted; when changed to sulfathiazole, the remaining coccus infection cleared up. The reverse of this also occurred in the series: a patient who improved symptomatically and the cocci disappeared on sulfadiazine, but in whom it was necessary to change to sulfacetamide in order to clear the bacillus infection.

Organisms Susceptible.—Under sulfonamide therapy all the following commonest invaders of the urinary tract are quickly overcome except in the relatively rare instances of sulfonamide-resistant strains: *Pseudomonas aerogenes, Proteus ammoniae, Escherichia coli, Aerobacter aerogenes, Staphylococcus aureus, Streptococcus faecalis;* other less usually encountered gram-negative organisms are also successfully dealt with as well as the organisms of brucellosis and bacillary dysentery, each of which has in rare instances been reported as the causative agent in urinary tract infection unassociated with a primary attack of the specific disease.

Reasons for Failure.—Enthusiasm for the use of the sulfonamides to the practical exclusion of all other drugs has run very high and it is difficult to find in the recent literature any satisfactory presentation of the subject of urinary tract infection as a whole; however, I believe I am justified in listing the following matters warranting consideration in connection with this new therapy: (*a*) Cases in which there is a drainage tube in place will clear symptomatically but the urine will not become sterile until drainage ceases. (*b*) It is practically impossible to sterilize the urine in the presence of an indwelling catheter. (*c*) Bladder tumors, other obstructions anywhere along the urinary channels, and particularly stones, will greatly hinder sterilization. (*d*) Any considerable amount of stasis along the tract (stasis is the important etiologic factor in the infections of pregnancy) will prevent sterilization, but it is said that the urine can be freed of bacteria even if there is a retention of as much as 3 ounces in the bladder; it requires less stagnation than this in the pelves and ureters to interfere seriously with the action of the drugs. (*e*) Closed pockets of pus (abscesses, pyonephrosis, etc.) usually defy sterilization. (*f*) When there is a high degree of bilateral renal deficiency it may be impossible to produce a therapeutic level of sulfonamide in the urine without piling up a dangerous amount of the drug in the blood stream. (*g*) Crabtree (1941) said that in severe degrees of either acute or chronic infections of one kidney there is a tendency for the drug to escape so completely through the uninfected functioning kidney that an effective concentration in the affected kidney is not obtained.

Dosage and Fluid Intake.—Dosage has decreased since the earlier studies. For example, Cook said, in 1940, that he thought the 60-grain (4 Gm.) daily dosage originally used could be well reduced to 45 grains (3 Gm.) and, in 1941, he said he had been using no more than 30 grains (2 Gm.). Alyea (1942) used the following plan: 30 grains (2 Gm.) a day for ten days, but if after three days there is no improvement the patient is changed to one of the other sulfonamides. In some instances he continues the drug five days longer than the usual period at 1 Gm. a day, and in others he stops for a week and then gives a second course of 2 Gm. a day for five days. Alyea and Parrish (1943) used 45 grains (3 Gm.) the first day and 30 grains (2 Gm.) a day for seven days

thereafter. Helmholz (1941) stated that at least for *Escherichia coli* infections 12 to 15 grains (0.75–1.0 Gm.) per day should suffice in average cases; he also felt that 2 grains (0.13 Gm.) five times daily should prevent the infections commonly associated with postoperative catheterization. All observers are agreed that fluids should be forced during the period of sulfonamide administration; the adult patient should receive at least 3000 cc. of fluid daily.

Sulfasuxidine, employed by Everett *et al.* (1945), must be used in daily dosage as high as 0.25 Gm. per kilogram of body weight; the authors found this high dosage objectionable from the standpoint of expense to the patient and stated that they are currently investigating phthalylsulfathiazole (sulfathalidine), with which they hope to accomplish the same results with a dosage of no more than 0.1 Gm. per kilogram of body weight daily.

Methenamine.—Methenamine (urotropin) is excreted unchanged by the kidney and is not itself bactericidal, but when it enters acid urine formaldehyde begins to be split off and gives the urine its bactericidal properties. Helmholz has shown that the proper condition for its greatest activity is a urine of *p*H 5.5 or less. Since chlorphenol red paper, or nitrazine paper (Squibb) indicates this degree of acidity, the practitioner's problem simply consists in maintaining a urine which will give a positive test with this paper while he is administering methenamine. The drugs principally used for this acidification have been sodium acid phosphate, ammonium acid phosphate, ammonium nitrate and ammonium chloride; ammonium acid phosphate has been shown to be the best acidifier and to cause the least gastro-intestinal irritation. Usual adult dosage is 30 grains (2 Gm.) of the acidifying drug and 15 to 20 grains (1–1.3 Gm.) methenamine four times daily. Helmholz's (1937) method of using these drugs in children is a good model to follow for patients of any age. He begins with the acidifying salt alone, 7½ to 15 grains (0.5–1 Gm.) four times daily, and then when the urine reaches *p*H 5.5 starts giving methenamine, 2 to 3 grains (0.15–0.2 Gm.) four times daily for infants, 5 to 7½ grains (0.3–0.5 Gm.) for children of four to five years, and 12 to 15 grains (0.75–1 Gm.) for children of six to fifteen years. Unless there is evidence of some injury by the drug, which is unusual (frequency, hematuria, pain, skin rashes, excessive gastro-intestinal irritation), he continues the dual medication as long as is required to produce and maintain a negative urine; *i.e.*, the urine is cultured at forty-eight hours, and again each twenty-four hours, and each time that it is found positive in the presence of *p*H 5.5 he increases the dose of methenamine 4 grains (0.25 Gm.) per dose. In any case, even though the culture is negative very early, the drug is administered for five or six days. Helmholz feels that to attempt treatment without control by culture is pure guesswork since the urine may be rendered sterile in twenty-four hours or it may not become sterile in two weeks; however, it hardly seems likely that practitioners working under average conditions will be able to achieve quite this high ideal of basing methenamine administration on the result of repeated twenty-four-hour cultures of the urine. It is generally agreed that the drug is more often effective in bacillary than in coccal infections, though some strains of *Escherichia coli* are extremely resistant.

Mandelic Acid.—In mandelic acid Rosenheim found an organic acid which, escaping oxidation in the body, is excreted intact to give bactericidal properties to the urine. It is nowadays rarely used except in sulfonamide-resistant cases, but Burns (1944) felt that since it is highly effective against *Streptococcus faecalis* it should always be a preferred drug in infections with this organism.

Mandelic acid may be given in the form of the elixir, syrup, or tablet. When given in the form of the tablet, acid salt must be prescribed along with it as in the case of methenamine (see above); the adult dose is 45 grains (3 Gm.) at six-hour intervals, 4 doses—a total of 180 grains (12 Gm.)—in the twenty-four hours. Burns (1944) preferred to use it in the form of the syrup or the elixir. The average adult dosage of the syrup he stated to be 2 teaspoonfuls four times daily and of the elixir 1 teaspoonful four times daily. Many men like to use the drug in the form of calcium mandelate, which is tasteless and does not cause much gastro-intestinal disturbance; it is said that it will often also give a sufficiently acid urine so that acidifying salts need not be used with it. Helmholz's method of using this agent may serve as model procedure: for children up to three years, 7½ to 15, or even as much as 20 grains (0.5–1 or 1.3 Gm.), four times daily; from four to eight years, 25 grains (1.5 Gm.) four times daily; children more than ten years may be started on 40 grains and can tolerate up to the full adult dose. The drug is said to be well flavored by prescribing it in solution in compound syrup of sarsaparilla, and also that if this is diluted with charged water at the time of taking, root beer is very well imitated. The conditions are the same as in the case of methenamine so far as duration of therapy, culturing of urine, and so on, are concerned.

I have not seen the record of a satisfactory clinical study of the newly proposed drug methenamine mandelate. Sodium mandelate in 20 per cent solution adjusted to a *p*H of 7.2 was given intravenously by Carroll and Coleman (1943) in 110 injections to 36 patients. They found 25 cc. of the solution to be well tolerated and to produce sufficient concentration to be therapeutically effective for eight hours after the injection. This interesting work is still entirely in the experimental stage.

Neoarsphenamine.—Neoarsphenamine, used in the same manner as in the treatment of syphilis, can sometimes be relied upon to clear up coccal infections that have resisted the other drugs. Its potential toxicity, however, is comparatively so much greater than the others that I think no one advocates its trial as the primary agent in any case nowadays.

Penicillin.—From the experimental standpoint, Helmholz and Sung (1944) concluded that the bactericidal action of penicillin at the low level of its concentration in urine when it is given systemically presents theoretic possibilities for the treatment of infections due to *Staphylococcus aureus*, *Streptococcus faecalis* and *Proteus ammoniae* and that the resistance of *Escherichia coli*, *Aerobacter aerogenes* and *Pseudomonas aeruginosa* to penicillin practically rules it out as a means of treating these infections.

Local Application of Urinary Antiseptics.—The sulfonamides are sometimes introduced into the renal pelvis directly through the ureteral catheter; this is apparently an effective type of therapy in selected cases; Austen (1940) showed that absorption of appreciable amounts into the blood stream can take place when the drugs are administered by this route. The sulfonamides are also used in 0.8 per cent solution for continuous irrigation or several times daily lavage of the bladder. Pinck *et al.* (1944) found that if sodium citrate solutions are introduced for anticoagulant action in the tract at the same time as sulfonamides the bacteriostatic activity of the latter—at least of sulfacetamide, the drug they experimented with—will be nullified. The older solutions used for bladder irrigation are the following: silver nitrate, 1:10,000–1:5000; potassium permanganate, 1:8000–1:5000; mercurochrome, 1:200; mercurophen, 1:10,000; gentian violet, 1:500; acriflavine, 1:8000–1:6000. Reynolds and

Schulte (1943) felt they obtained good results from the installation twice weekly of 2 ounces of cod liver oil especially in patients with infected residual urines.

STONE IN THE URINARY TRACT

Kidney stones, or calculi, consist of amorphous collections of granules of urinary salts gummed together and embedded in a structureless albuminous substance. When their presence is made known they may be large or small and may be embedded or lying free in the calices or pelvis of the kidney, or they may present as a foreign body obstructing the ureter. At times there is but a fluctuating aching pain in the loin of the affected side, or radiating into the lower back, the abdomen, or leg. Constant or intermittent hematuria is oftentimes remarked, and sometimes there is the passage of "sand." Bladder symptoms, such as frequency, urgency and burning, are not unusual even when the bladder is free from lesions. The most characteristic manifestation of the presence of stone, however, is an attack of renal colic. The pain strikes quickly in the kidney region, but soon radiates down into the abdomen, the thigh and leg, the scrotum (or vulva), and sometimes into the opposite kidney region (the so-called "renorenal reflex"). There is nausea, vomiting and gaseous distention during such an attack, which may last for a few minutes to several days, but probably endures for four to twelve hours in most instances. If complete obstruction occurs there will be hydronephrosis on the affected side and perhaps anuria, even though the opposite side is not obstructed (the so-called "reflex anuria"). Thus, the symptoms of renal lithiasis are the symptoms of obstruction, but why the stones form in the first place is one of the most venerable of medical mysteries. The disease is unilateral in most cases, but at the present time there is no way of foretelling the tendency in a patient to develop stones on the other side. Stones in the bladder may be either kidney stones halted there by obstruction, or they may originate there as deposits on some introduced foreign substance or as encrustations on inflammatory lesions. In general the symptoms of stone in the bladder are not very characteristic. The most usual complaints are of frequency, hematuria, the passage of sand, difficult urination, sudden stoppage in the flow of urine, and pain running down to the head of the penis. Tuberculosis, prostatic enlargement and vesical neoplasm must be carefully ruled out.

The earliest known urinary calculus was found among the pelvic bones of a boy about sixteen years of age in an Egyptian grave of a period some time prior to 4800 B.C. The treatment of vesical stone was made a specialty early in the Middle Ages by quacks who "cut" only for stone, most of the operations being performed on children, and these operative procedures were not effectively got out of their hands until the sixteenth century. In our present era, vesical calculus is predominantly a malady of elderly men, at least in the highly civilized countries, but it is said to occur still with great frequency in the young in hot dry climates. Urinary calculi occur much less frequently among Negroes than among whites; the incidence in all races is said to be very low in wet tropical countries, though it was said by Glazier and Olson (1944) to have been rather high in the South Pacific area during War II under battle conditions in which there was excessive perspiration and a reduced fluid intake with

resultant highly concentrated and highly acid urine. Apparently Domenico Marchetti, in 1633, performed the first operation for renal calculus.

THERAPY

I shall not review all the diverse views regarding the etiology of stone because to do so would require a great deal of space and perhaps in the end really not greatly enlighten the reader. However, the possibility that Randall (1944) is correct should be mentioned: he says that no matter what dyscrasias, deficiencies, or what not dictate the deposition of particular salts, there is in every case of primary renal calculus a typical microscopic pathologic process in the wall of the renal papilla which precedes the gross appearance of stone—and he has convinced himself at least that this is true.

Fluids.—The opinion is unanimously held that the forcing of fluids is indicated for all kinds of stone since the more dilute the urine the less chance there is for precipitation of salts to occur. Contrary to prevalent opinion a dilute urine does not preclude an acid urine.

Infection and Stasis in the Urinary Tract.—Both these conditions are known to contribute to calculus formation. The sulfonamides are proving a boon in clearing up such infections; fortunately they are effective against the common urea-splitting organisms which enhance precipitation of phosphates and carbonates by increasing the alkalinity of the urine. Stasis is a matter often requiring the most expert urologic handling.

Hyperparathyroidism.—A few years ago, Albright and his associates at the Massachusetts General Hospital showed that tumors of the parathyroid glands giving rise to high blood calcium, with or without other signs or symptoms of hyperparathyroidism, are sometimes associated with recurrent stone, and that surgical removal of such tumors may correct the lithiasis. However, Griffen *et al.* (1938) found hyperparathyroidism to be an etiologic factor in less than 0.2 per cent of 1206 cases of renal calculus at the Mayo Clinic.

Vitamin A Therapy.—The Council on Pharmacy and Chemistry, in 1945, still does not accept the contention of Higgins, of the Cleveland Clinic, that high vitamin A feeding is of considerable value in dissolving and preventing the recurrence of stones. Higgins employs in addition to vitamin A (see Xerophthalmia for methods) an acid-ash diet. Oppenheimer and Pollack (1937) studied this matter very thoroughly in 27 patients at the Mount Sinai Hospital in New York and failed to confirm Higgins' findings; in none of the patients did the calculi show even partial solution though the patients were on the diet for from six to sixteen months; in 5 the size of the calculi increased, and in 1 a new stone formed. Erickson and Feldman (1937) failed with the Higgins regimen in their 11 patients who remained faithful to the treatment for six to nine months. Jewett *et al.* (1943) failed to find any evidences of vitamin A deficiency in 20 patients with urolithiasis, and in the autopsies of 78 patients who had had stone, they found no evidence of the epithelial metaplasia in the respiratory and urinary tracts characteristic of vitamin A deficiency. Lassen (1942) also failed to find any evidences of such deficiency in calculus patients in Denmark. However, it should be pointed out that in the patients of Erickson and Feldman, and also in those of Long and Pyrah (1939), vitamin A therapy did not raise the systemic vitamin A reserve as it normally does in patients not afflicted with stone. This is interesting, as are also the facts that: (*a*) in Syria, according to Brown and Brown (1941), the vitamin A intake is low and the incidence of vesical stone in children is high; (*b*) the South African native

Negro (Bantu) does not form stone, according to Vermooten (1937), and his diet is rich in vitamin A, has an acid ash and is extremely low in calcium. Perhaps there is a kernel of truth buried somewhere in this vitamin A deficiency theory.

Recumbency.—It is now agreed that an active individual who has been using calcium constantly in renewing bone structure is in danger of developing stone when he becomes inactive or is incapacitated by a bout of illness or through immobilization in a cast; calcium and phosphorus are released from bone under these conditions and their concentration in the urine greatly increased In addition there is likely to be stasis somewhere along the urinary tract, at least at intervals, in such individuals, which invites both infection and stone formation. The prophylactic measures to be taken in such cases consist in pushing fluids and changing posture as frequently as is possible consistent with orthopedic or other considerations. Leadbetter and Engster (1945) said that patients in body casts or with spinal cord injuries should be turned every two or three hours and that if possible the head and upper portion of the body should be elevated for periods each day to assist in emptying the renal pelves. Boyd (1941) advocated placing patients for at least an hour or two daily on the ventral surface of the body and having them drink a large amount of water before shifting into this position. Active movement and massage of all limbs not splinted is to be practiced daily.

Calcium Phosphate Stones.—In addition to pushing fluids the usual procedure is to use in these patients a diet with an acid ash (see "Diets") in order to keep the salts in solution; theoretically the dissolution of the stone itself might occur in this acid urine. However, it is also to be remembered that an acid-ash diet will also cause loss of calcium and phosphorus from the bones and thus increase the concentration of these elements in the urine; Flocks (1941) warned that in some instances, *i.e.*, if the urinary calcium is high (daily normal, 200 mg.) in the beginning, one should use the acid-ash diet with great caution for fear the bad might outweigh the good effects. Albright (1937) pointed out that if an acid urine (a *p*H of 5.5 is usually sought) is not obtained then certainly the results will be bad, for the acid-ash diet will liberate salts from the bones which will be precipitated in the alkaline urine (infection with urea-splitting organisms is of course the greatest factor working against achievement of an acid urine). A measure often taken is to use acidifying drugs (see Urinary Tract Infection) in addition to the diet, but upon the whole this has not been helpful because the increased acidity of the urine has been paced by the increased liberation of calcium and phosphorus from the bones. It has been stated upon occasion that the Sippy regimen as used in peptic ulcer, and the self-prescribed alkali dosing of many dyspeptics, tend to promote the formation of calcium phosphate stones, but exact studies of this point have yielded findings strangely at variance: in Eisele's (1940) 505 patients with stone there was a history of treated peptic ulcer in 8.5 per cent; in Kretschmer and Brown's (1939) series of 1260 patients there was a similar history in only 1.2 per cent.

Dissolution by Retrograde Irrigation.—In recent years the group about Albright at the Stone Clinic of the Massachusetts General Hospital has been studying the possibility of dissolving stones by irrigation with a citrate solution from below. Their early solutions were too irritating, but Suby and Albright (1943) devised their "solution G" (page 776) with which they effected the partial or complete dissolution of calculi in 6 cases. The main object of treat-

ment with this solution is to keep it in contact with the stone as much as possible; of course the details of the actual type of irrigating tube and the like by which this is accomplished belong in the field of urological surgery. Suby and Albright made the point very emphatically that before attempting to dissolve a stone with their solution it is necessary to know that one is actually dealing with a phosphatic stone, by which is meant one composed of calcium phosphate with or without calcium carbonate or magnesium-ammonium-phosphate or both. Abramson (1943) reported the successful employment of this irrigation method in dissolving a large bladder calculus

Solution G (Suby and Albright, 1943)

Citric acid (monohydrated)	32.25 Gm.
Magnesium oxide (anhydrous)	3.84 Gm.
Sodium carbonate (anhydrous)	4.37 Gm.
Water to make	1000 cc.

of the phosphatic type in a case in which surgical intervention might have proved fatal, and Hamer and Mertz (1944) successfully used it for the removal of multiple calculi left behind after a pyelolithotomy. Sauer and Neter (1943) also employed the solution in an unspecified number of patients with late radium reactions in the bladder of the sort that are frequently complicated by formation of alkaline incrustations at the site of the ulceration, and said that the results accomplished "were impressive." These latter observers, however, felt it difficult to evaluate the extent to which improvement in their patients was due to the direct antimicrobial action of solution G.

Uric Acid Stones.—The treatment consists in using an alkaline-ash diet (see below) because the urates thus formed are more soluble than uric acid itself. Many of these patients have gout, a few have not; in all, the usual practice is to employ the low purine diet.

Calcium Oxalate Stones.—Since calcium oxalate is soluble both in acids and alkalis, nothing is to be expected from an attempt to change the reaction of the urine. Fluids are to be pushed. It is the practice in some quarters to prescribe a diet low in oxalates (see below), but I do not know how many men are willing to guarantee nonrecurrence of the stone as a result of using it.

Cystine Stones.—The patient with cystine stones is the victim of an hereditary disturbance in cystine metabolism. Cystine precipitates in an acid urine, so the treatment consists in using an alkaline-ash diet (see below).

Diets.—The several diets referred to above are the following. *Acid-ash:* meats, fish, eggs, cereals, little fruit and vegetables, no milk or cheese. Albright (1941) seems to feel nowadays that the adult, particularly if he is sedentary, should not drink milk or eat cheese even though he has *not yet* shown any stone tendency. *Alkali-ash:* fruits, vegetables and milk; as little meat, fish, eggs and cereals as possible. *Low purine:* (see Gout). *Low oxalate:* no potatoes, beans, spinach, tomatoes, beets, endive, rhubarb, asparagus, strawberries, raspberries, pears, plums, figs, currants, cocoa, chocolate, tea and sweets in general. MacDonald (1936) favored the use of hard cider for its malic acid content.

Spa Treatment.—The drinking of large quantities of water, frequently referred to above, has been asserted to be of value since ancient times. Certain mineral springs, of which every continent has its favorites, are said to have the power to fracture stones, with the fragments being ultimately passed;

at the least, much water is drunk at the spas and the music is often most enjoyable.

Surgery.—There is nothing to say in a book of this sort of course except to lament under this head the fact that a woefully large proportion of the victims of stone must still submit ultimately to instrumental or operative interference. Recurrence, however, is as much a bugaboo to the surgeon as to the internist.

Renal Colic.—In the presence of severe pain, morphine sulfate, $\frac{1}{4}$ grain (0.015 Gm.), or dilaudid, $\frac{1}{32}$ grain (0.002 Gm.), combined with atropine sulfate, $\frac{1}{100}$ grain (0.0006 Gm.), is given hypodermically; often the opiate has to be repeated and frequently will not relieve this pain at all. Colston (1936) felt that on the basis of opium's ability to stimulate ureteral musculature it would be much better to use atropine in combination with a sedative. I should think that the new drug demerol, with its ability to relieve smooth muscle spasm, may be expected to win a fine place for itself in the treatment of this type of colic; average dosage is $2\frac{1}{2}$ grains (150 mg.). Bauer *et al.* (1931) injected 20 cc. of 5 per cent calcium chloride solution intravenously in a small series of cases; in nearly all instances relief was prompt and great enough to permit the patient to go to sleep without an opiate; in 1 case calcium chloride injection succeeded where morphine had failed. Fleischman (1939) also reported success with the use of calcium chloride injections in a number of instances. Kirwin *et al.* (1944) felt that a deproteinated pancreatic tissue extract (depropanex) was effective in relieving the pain in some cases. Lund and Zingale (1943) used a synthetic hydrocarbon antispasmodic, methylamino-iso-octene (octin) with some degree of relief in a large proportion of their patients. Heat, best applied by placing the patient in hot water in the bath tub, is often effective in relieving this pain, but some individuals are in such agony that they cannot remain in the tub. Sometimes resort to general anesthesia is necessary. O'Conor (1939) gave subcutaneous injections of 1 cc. of 1:2000 solution (0.5 mg. of the active substance) of prostigmin methylsulfate at three- to four-hour intervals for four doses in 52 patients in whom surgical procedures were not critically indicated and cystoscopic manipulative measures had not been successful; he felt that passage of the stone was hastened in a good many instances but of course there was no way in which to make sure of this. Prostigmin's action would be just the opposite of that of atropine, *i.e.*, instead of relaxing the ureter it would stimulate its propulsive action; I should think one would have had to make certain in each case that the ureter was of normal conformation and completely unobstructed below the stone before beginning the use of this drug.

PROPHYLAXIS OF VENEREAL DISEASES

LOCAL MEASURES FOR THE MALE

As Applied by Trained Personnel.—It was the feeling among most of those who had to do with these matters during War I that locally applied prophylactic measures were successful in bringing about a marked reduction in the incidence of all three of the principal diseases, syphilis, chancroid and gonorrhea. Moore of John Hopkins Hospital, who was the inspector of the prophylactic stations in Paris and had 25 of the 72 under his immediate control, made

a statistical study of the results and believed that the man who failed to take the treatment was more than seven times as likely to contract disease as the man who did take it. He found that the earlier it was applied the more effective it was, the difference in its value when applied six or seven hours, for example, after exposure rather than one hour being very great; but he thought it still worth while giving, especially for protection against syphilis, even as late as twelve hours after. But this enthusiasm of Moore was specifically for one method only, namely, the presumably expert application of the prophylactic measures by trained soldier attendants in prophylactic stations. Greenwald (1943), writing during the height of War II, stated that the local measures were still held to be effective in the Army with respect to syphilitic and gonorrheal infections but that a disproportionately large number of individuals had developed chancroid despite the application of local prophylactic measures. I think it should be stated also that Boyden (1936) showed that local prophylaxis failed on the Asiatic Station of the U. S. Fleet, and that Parsons (1941) stated that at the time of his writing these measures were employed in the Navy as a sort of superfluous ritual, much like "the use of the finger bowl at the conclusion of a meal."

Standard Method.—As a first step the patient is instructed to urinate and then, being provided with a pint of warm water in a basin and a gauze wipe, he washes thoroughly, while the attendant drops liquid soap on the penis. The next step is the injection of 1 drachm (4 cc.) of 2 per cent protargol or 10 per cent argyrol solution into the urethra by the attendant. The patient then holds the meatus firmly between the thumb and forefinger for five minutes, from time to time allowing a drop to escape from the meatus so that all parts of the urethra are kept in contact with the solution. At the end of five minutes, the solution is allowed to escape without pressure so that a few drops remain. One-half drachm (2 Gm.) of $33\frac{1}{3}$ per cent calomel ointment is next rubbed thoroughly by the patient, under the observation of the attendant, into all parts of the penis for five minutes, special attention being paid to the retracted prepuce, the frenum and the glans. Finally the penis is wrapped in toilet paper to protect the clothes, and the patient instructed not to urinate for four or five hours.

Suggested Modifications.—In an experimental study in which chancroids were induced by inoculation into human volunteers of strains recently isolated from fresh chancroids, Greenblatt *et al.* (1943) found that when a mixture of 20 to 33 per cent of a sulfonamide was added to the calomel ointment the success of the local prophylactic measures against chancroid was greatly increased, and they felt that further study of this simple modification was worth while; under field conditions in the Navy in which 10,368 prophylactic treatments were given, Zeve and Schneierson (1944) found that the addition of a sulfonamide did indeed greatly enhance the protective ability of the ointment against chancroid, their mixture being one third of a 5 or 10 per cent sulfanilamide or sulfathiazole ointment and two thirds calomel ointment.

In comparison with the silver salts and calomel ointment as used in the standard treatment, both Taylor (1943) and Blute (1944), as a result of experience in relatively large series of cases, found the following formula to be superior:

Mercury oxycyanide	0.20
Sulfathiazole powder	10.0
Tragacanth	10.0
Water	225.0

The emulsion, which should be of a heavy creamy consistency, is kept in a jar and freshly prepared every month. In using it, 5 cc. are injected into the urethra, held five minutes, and then emptied and the remainder removed by a syringeful of liquid petrolatum and by urination in order to prevent the chemical urethritis which will result from prolonged intimate contact of the mixture with the urethral mucosa. About a gram of the emulsion is then rubbed over the skin of the penis, scrotum and thighs; the clothing is not stained.

As Self-Applied.—Moore found in War I that the application of prophylactic measures by the soldier himself in the prophylactic station is of no worth, and at that time the prophylactic packet was almost universally declared a failure also. In War II, however, Turner and Brumfield (1944) pointed out that prophylactic stations were not often well adapted to the needs of the Army and that with modern transportation soldiers were enabled to scatter over wide areas during the course of a weekend, so that no dispensary system could provide convenient facilities for the majority of individuals. In order to meet this problem therefore, pocket kits containing essentially the same chemicals employed in station prophylaxis were developed and made readily available to personnel. Whether this return to the prophylactic packet will in the end be found to have been worth while remains to be seen.

LOCAL MEASURES FOR THE FEMALE

Moore's Method.—"Have the patient urinate. Place the patient in the lithotomy position. Wash the genitals and adjacent parts with soap and water. Give a douche of 2 quarts of sterile water, temperature 100° F., followed by 2 quarts of 1:2000 mercuric chloride solution, and wash external parts with the latter. Dry the vagina and vulva by sponging. Swab the entire vagina, through a speculum, with a 2 per cent protargol solution, or 10 per cent argyrol solution, freshly made; reach every fold and especially the posterior vault and external os. Swab the entire vulva in the same way, reaching every recess and endeavoring to facilitate the entrance of the solution into the openings of Skene's ducts and Bartholin's glands. Inject enough of the same solution into the urethra to distend it moderately and let the patient hold her finger (in a rubber glove) against the meatus to retain the solution for from three to five minutes.

"Douche the vagina and vulva with a small amount of sterile water, and sponge dry with gauze. Apply calomel ointment to the cervix, vagina, vulva, and adjacent parts, rubbing thoroughly into the recesses and folds of the mucous membranes and skin, and taking at least ten minutes for the operation. Do not use more than 4 Gm. (1 drachm) of calomel ointment in the vagina. Cover the external parts with oiled silk or waxed paper securely and instruct the patient to allow ointment to remain for several hours before washing the parts."

CHEMOTHERAPEUTIC MEASURES

Sulfonamides.—I shall cite two studies of larger scale that have come to my attention, both performed during War II and neither perfect in control. Loveless and Denton (1943) gave a company of approximately 1400 troops sulfathiazole prophylaxis of 2 Gm. before leaving the fort on pass. Those taking station prophylaxis received no further drug, but all others received

4 additional grams, 2 on returning to the fort and 2 on the next morning. The gonorrhea rate in the company dropped to a level of 8 per 1000 yearly as compared with 171 per thousand in a control group of approximately 4000 troops at the same post. The reader will do well to note carefully, I think, that these were all Negro troops since it is agreed by all that Negroes are much more susceptible to the action of sulfonamides in gonorrhea than are whites. The chancroid rate dropped to 6 as compared to 52 in a control group. In the study of Keet (1944) a prophylactic dose of 1 Gm. of sulfathiazole was given orally within twelve hours after intercourse in 1802 Navy personnel as compared with an untreated control group of 503 similarly exposed. The incidence of gonorrhea in a sulfathiazole-treated group was approximately 1 to 120 exposures, in a control group 1 to 39 exposures; the incidence of chancroid in the treated group was 0, in the control group 1 in 101 exposures. None of the individuals in either the treated or untreated groups were Negroes and in some of them other local prophylactic measures had been employed, so it is rather difficult to assess the value of these findings at least in comparison with the study described above.

In the experimental studies of chancroid of Greenblatt *et al.* (1944), above referred to, sulfathiazole administered orally following inoculation, before inoculation, as well as before and after inoculation, prevented the production of experimental chancroid but only if no more than three to five days were allowed to elapse before the experimental inoculations were performed.

Speert (1943) suggested an intravenous maternal injection of sodium sulfathiazole or sodium sulfadiazine to protect the fetus prior to delivery when the lower genital tract of the mother harbors the gonococcus. Gleich *et al.* (1944) proposed the administration of sulfathiazole to the newborn infant as a prophylactic measure against ophthalmia neonatorum. Their dosage was 3 grains (0.2 Gm.) as an initial dose and then 1 grain (60 mg.) every four hours to a total of 20 grains (1.2 Gm.); in 1425 infants so treated only 2 cases of gonococcic conjunctivitis developed; both of these were in infants who had received a total of only 14 grains of the drug, while at the same time in 1262 untreated infants 6 cases developed.

Arsenicals or Bismuth.—There is now unanimous agreement among students of this subject that the administration of a few doses of an organic arsenical, or a bismuth preparation, after a suspicious exposure is not a desirable thing for the reason that it can prevent the development of the primary sore but not the infection, thus leaving the patient, as Harrison expresses it, "in a fool's paradise." With the results of treatment of seronegative primary syphilis being what they are today, the approved line of action is to wait for the appearance of a chancre before proceeding to institute treatment.

DISEASES OF THE NERVOUS SYSTEM

SYDENHAM'S CHOREA

(*St. Vitus' Dance*)

Chorea is one of the common diseases of childhood. It may occur at any age but most cases are seen between the fifth and fifteenth years. The disease is more frequent in occurrence in girls than boys and in the poorer than in the richer classes. Negroes and full-blooded American Indians are rarely affected. When the child is brought to the physician for the first time, the parent usually states that for a week or more it has been fidgety, emotional and excessively clumsy. Upon observation the patient will be seen to be in almost constant jerky motion; grimacing and purposeless movements of the face and head are the most usual phenomena, but any part of the body may share in the wriggling or writhing motion. There is also much muscular incoordination, as shown frequently by the overpassing of objects with the hands or by difficulties in locomotion. Except in the most severe cases, these movements cease during sleep and are to some extent under voluntary control; at least firm, kindly commands will often cause them to be restrained for a brief space. The speech is often choppy in character, sometimes being entirely unintelligible; in a relatively few cases the child is entirely unable to speak. The usual mental involvement is in the direction of dulness, carelessness and loss of memory, though not infrequently this state is broken into by intense emotional storms. Appetite and the general condition usually remain good despite some loss of weight and the development of more or less anemia. Headache and muscular weakness are always complained of. The most frequent complication is endocarditis. The duration varies from several weeks to many months, sometimes to more than a year. Death is very rare, and when it occurs is due to general wasting plus intercurrent sepsis and heart failure. Relapses and recurrences are not uncommon in this disease.

Since the middle of the last century the effort has been made, both in Europe and America, to link together rheumatic fever and chorea. Undoubtedly the presumptive evidence in favor of such an association has great weight but the contention is not yet proved. This much seems to be established, however (Parrish *et al.*, 1937; Sutton and Dodge, 1938; Usher, 1938): the child with chorea will develop the rheumatic type of heart disease in from 20 to 50 per cent of instances even though he does not develop the typical joint and other symptoms of acute rheumatic fever. Chorea has also many times been seen to follow an attack of one of the other infectious diseases, particularly scarlet fever, a disease also thought to be of streptococcal origin.

Sydenham provided the classical description in 1686. During the early part of the fifteenth century, one of the waves of crazy fanaticism which characterized the period took the form of a dancing mania among certain groups of physically degenerated people; one such group, "dancing" toward the chapel of St. Vitus in Zabern, gave the disease its other title—though the etiology of this affair of perverted crowd psychology bears probably no relation to that of the disease we have here under consideration.

THERAPY

Rest.—Absolute bed rest is the most important single element in the treatment of chorea, not only because it seems to promote subsidence of symptoms but also because of the possibly associated rheumatic fever and the ever-lurking endocarditis. Howell (1935) stressed the importance of keeping children and other visitors away and of keeping the room darkened. Whether this rest should be secured within or without the family circle must be decided in each individual case. The sedative drugs (for a list, see Insomnia) are by no means contraindicated and can perhaps be used with profit in most severe cases; of course their dosage must be reduced according to the child's size and age. Poynton added chloretone to the list of useful sedatives in this disease, 5 grains (0.32 Gm.) three times daily. In some cases, Howell gave 5 to 10 grains (0.3–0.6 Gm.) urethane. At times general anesthetics must be employed; Slot and McDade (1933) gave 1- to 2-cc. intravenous injections of evipal sodium, Cole (1936), avertin rectally, 0.1 Gm. per kilogram body weight. Duckett Jones (1935) strongly advised the trial of stramonium, powdered (not as tincture), before resorting to these more heroic measures in violent cases. Tepid sponge baths are nearly always soothing, and in some instances an excellent reaction follows upon the use of the ice pack in uncomplicated cases (*i.e.*, wrap the patient in blankets with, next to his skin, a sheet wrung out of very cold water).

Salicylates.—Those who look upon chorea as a rheumatic meningo-encephalitis consider the salicylates to be indicated. For a description of their employment, see Rheumatic Fever. Mutch (1934) preferred calcium aspirin for its alleged triple action: antirheumatic, sedative, corrective of calcium deficiency. As a matter of fact, I know of no studies that prove the salicylates to be of direct value in chorea.

Arsenic.—This drug has been employed empirically for many years. Usually it is given in the form of Fowler's solution (the solution of potassium arsenite of the U.S.P.) in ascending doses. The method most often employed is to begin with 3 minims (0.2 cc.) three times daily and increase this dose by 1 minim (0.06 cc.) each day or every other day, until 10 minims (0.6 cc.) are taken at each dose; this dose is then continued for a week unless toxic symptoms appear earlier. The symptoms most often presenting are puffiness under the eyes or about the ankles, or gastro-intestinal disturbances. The possibility of arsenical neuritis should always be borne in mind, however, for this rather serious consequence of prolonged arsenical therapy has been seen, without any premonitory edematous or gastro-intestinal symptoms, more often than is commonly believed. I know of no statistical studies of the efficacy of arsenic treatment; the presumptive clinical evidence is far from being unanimous in its favor. Of course the disease is almost too variable in severity and course to make careful studies of nonspecific remedies possible; however, Abt's statement, made in 1916, would probably find more endorsers today even than it did at that time: "I want to say a word about arsenical treatment and rest in bed. For years I have had children brought to me with chorea. One of my colleagues might have a case in an opposite bed. I would say, 'You treat with arsenic and I will treat without.' The baby without arsenic, but with rest in bed, would recover just as rapidly as the other child treated with arsenic. The child's term in the hospital would be no longer than with the arsenical treatment. . . . It seems to me the treatment of these cases of chorea, especially in neuropathic children without heart lesions and no evidence of infection, is to

take them away from their family, feed them, keep them absolutely quiet in bed, give them hot baths, and they generally recover in a short time."

Nirvanol.—It has been claimed that this drug is often effective in sharply checking chorea, but it is a very toxic agent and the great majority of observers feel that the fever reaction, which is probably all that is accomplished with nirvanol, is more safely induced by other measures.

Fever Therapy.—Since 1931, Sutton and her associates have been treating cases by induction of hyperpyrexia. In the beginning they used typhoid-paratyphoid vaccine intravenously, beginning with 0.05 or 0.1 cc. and determining the subsequent daily dosage by the reaction, the aim being to attain a temperature of 104° to 106° F. (40° to 41° C.). If necessary they administered a second dose on the same day and continued treatment, with occasional days of rest, until all signs of chorea disappeared. Latterly it has been recognized that the physical means of producing fever are equally effective and cause the patient less discomfort; there are now a great many observers who testify to the value of the hypertherm in this disease. Most cases are said to respond favorably and quickly, but the technic does not yet seem to be uniform: some men give treatments at 104° to 106° F. (40° to 41° C.) for two hours daily, others at only three- or four-day intervals; in Bennett and Hoekstra's (1941) 17 cases, an average of eight daily treatments was necessary to effect cure. The consensus is that cardiac involvement does not contraindicate fever therapy.

HICCUP

Hiccup is produced by a sudden clonic spasm of the diaphragm accompanied by a spasmodic closure of the glottis. It occurs not infrequently in the fetus, detectable as regular, short, quick jerks at the rate of 15 to 30 a minute; they are visible and palpable, and the muscle sound of the diaphragm as well as of the body striking the uterine wall can be heard. If occurring during labor it is sometimes not interrupted by the birth of the child and continues for a short time afterward; De Lee has seen a baby born hiccuping so loudly that it could be heard in the next room. McGee (1943) felt that fetal hiccup indicates that the child will in all probability be a very allergic infant. The greatest incidence of hiccup in infancy occurs during the first three months, principally among breast-fed babies, probably due to overdistention of the stomach with food and swallowed air. In adults it may be caused by inflammatory or pressure irritation of the phrenic nerve or reflexly through the vagus. It may be a symptom of almost any disease but the entities with which it is most often associated are neurosis, epilepsy, encephalitis, brain tumor, Addison's disease, and functional, organic, traumatic and acute infectious processes anywhere in the gastro-intestinal tract. Apparently it also occurs reflexly in diseases of the pleura and pericardium as well as in some of the chronic constitutional diseases. And some surgeons of experience, as pointed out by Wade (1932), look upon the occurrence of postoperative hiccup as a warning of impaired renal function. Byrnes (1935) described some cases apparently occurring as an unusual form of tabetic crisis. In addition to which there are the idiopathic and epidemic cases, the latter believed by MacNalty (1937) to be manifestations of epidemic encephalitis of a mild type.

Rosenow (1942) said that a large number of patients having both epidemic and postoperative types of hiccup had their attacks arrested following injections of "encephalitis antistreptococcic serum" which he was studying.

THERAPY

Most cases in infants are transitory and of no serious importance. The infant should not be permitted to suck the breast when it is empty or the bottle in such way as to take in large quantities of air, and after feeding it should be held upright to aid regurgitation. Sometimes it is necessary to give a spoonful or so of hot water or weak sodium bicarbonate solution or diluted fruit juice. Of course the more serious cases may also be seen in infants. In adults the most important thing, of course, is to make every effort to locate and treat the underlying cause of the trouble, which is very much easier to say than to do. The actual measures directed against the spasms are of course legion, as is the case in all maladies of vague and variable etiology; the following seem most often to have been of assistance.

Sedatives and Anesthetics.—The whole gamut is run—bromides, chloral, barbiturates, paraldehyde, belladonna, compound spirits of ether (Hoffmann's anodyne), hyoscine, opiates, apomorphine and the general anesthetics. Cadham (1925) said that benzyl benzoate found greatest favor with physicians during the well-known Winnipeg epidemics, but he felt that evaluation of any remedy was very difficult; this drug may be suspended with mucilage of acacia or prescribed in one of the higher alcoholic vehicles, such as the compound tinctures of cardamom, gentian, or cinchona (all of which have some carminative value), or the tinctures of sweet or bitter orange peel; Ruhräh preferred to give the drug in sweetened milk. See also the sedative measures employed in whooping cough; these are sometimes successful here also. Deep anesthesia is sometimes successful, but it was induced with both ether and chloroform in Campbell's (1940) case without effect either time.

Benzedrine (Amphetamine) Sulfate.—Shaine (1938) reported good results following hypodermic injection of $\frac{1}{6}$ to $\frac{1}{3}$ grain (10 to 20 mg.) of this drug.

Cocainization.—In persistent cases, Lichtenstein (1928) obtained good results with a dilute cocaine-epinephrine solution containing a very small amount of phenol, applied to both nostrils on pledgets of cotton.

Carbon Dioxide.—Carbon dioxide in various proportions with oxygen, delivered from the usual apparatus, has been very favorably reported upon a number of times. Golden (1931) described a simple, inexpensive method of inducing the inhalation of carbon dioxide, which has been much used by others since. An ordinary paper bag of medium size and strength is placed over the patient's face and so held that it tightly encloses the mouth and nose, thus inducing rebreathing of an atmosphere whose carbon dioxide content steadily rises. Five of Golden's 6 patients were relieved in from three to six minutes; one of them had been hiccuping for two days.

Fluids.—In postoperative cases in which impaired renal function is suspected, the "pushing" of fluids not infrequently brings relief.

Lavage.—Continuous siphonage of the stomach through the Levine tube has been successfully employed a number of times.

Phrenic Nerve Operations.—Weeks (1931) believed that in intractable cases, when everything else has failed, the patient should be examined fluoroscopically to determine which side of the diaphragm is involved; the phrenic nerve on that side should then be exposed under local anesthesia, a stout silk

ligature passed about it, and the nerve anesthetized—which seems to bring relief of about eight hours. Following this, traction is to be tried, and this failing the nerve can be crushed; failure of both points toward anastomosis below the site of section or blocking, and indicates avulsion. In cases of bilateral involvement, it is said that the operative procedures can be bilaterally performed. Campbell (1940) reported a case in which bilateral phrenicotomy was required for cure.

Household Remedies.—The remedies tried with varying degrees of success in mild attacks are pressure or application of an ice-cap on the back of the neck, holding the breath, swallowing a bolus of food, tickling the nose to induce sneezing, gentle compression of the upper part of the thyroid cartilage, sipping cold drinks, swallowing finely cracked ice, prolonged traction of the tongue, painting the uvula with an irritant such as tincture of iodine, inhaling fumes of ether or smelling salts, drinking some gastric irritant such as Worcestershire sauce or an ounce or so of whisky "neat," pressure on the upper lip or eyeballs or ribs, holding the breath, sudden fright.

TRIGEMINAL AND ASSOCIATED TYPES OF NEURALGIA

Trigeminal neuralgia is a disease of the gasserian ganglion, affecting one or all of the branches of the trigeminal nerve; the infra-orbital division is the most frequently affected, then the mandibular and then the ophthalmic. The pain comes "out of a clear sky," and is described as shooting, stabbing, lightning-like, cutting, etc. It lasts but a few seconds to a few minutes, but during the time of its presence is perhaps as severe as any that man is ever called upon to endure. The patient remains motionless with a fixed grimace and oftentimes with some defensive posture of the body as a whole. Relief is usually complete upon termination of the spasm. Such an attack may be precipitated by any minor essential movement, such as opening of the mouth, swallowing, winking, talking, washing the face, brushing the teeth, and so on. In the beginning there is often a considerable interval between seizures, and there may even be an asymptomatic period of several months to years, but finally in practically all cases the pain becomes continuous and affects all three divisions of the nerve. It is my belief that spontaneous recovery has never been recorded. In untreated cases, death may result from inanition consequent upon inability to eat or sleep. Rarely, very careful general and neurologic examination will be required to rule out peripheral lesions as the cause of this type of pain—lesions involving the nerve trunks, posterior roots or root ganglia, lesions of the brain stem or in the optic thalamus, lesions in higher associated brain centers. Woltman (1942) pointed out that tumors of the gasserian ganglion are not common but that when they occur the pain is usually constant and intense and not influenced by eating, speaking, or external irritation, and as a rule paresthesias and sensory changes appear relatively early. Typical of the sort of pseudotrigeminal neuralgia which may be encountered is the case of Banyai (1936) in which pain was completely relieved by phrenic nerve block and was thought to have been referred to the trigeminal nerve from the site of a tuberculous diaphragmatic pleurisy.

Tic douloureux involving the glossopharyngeal nerve is manifested as pain extending from the tonsillar region into the ear; relief of pain upon cocainiza-

tion of the nasopharynx establishes the diagnosis. Tic involving occipital nerves arising from the first, second and third cervical nerves is differentiated through relief achieved upon procaine infiltration beneath the scalp. Other, very rare, types are those known as Sluder's, Jacobson's and Hunt's neuralgias.

Trigeminal neuralgia, by far the most frequently encountered of these maladies, is almost always a disease of those in or past the middle years of life, though Harris (1943) said he had had more than 20 patients who began to suffer before the age of twenty-one—two of them at the age of twelve years and one at the age of sixteen months. It is a disease of unknown etiology, though its association with carious teeth has often been remarked; Harris (1936) stated that an hereditary tendency is not rare. The entity was first described by Avicenna (Ibn Sina), he who was called "the Prince of Physicians" at the court of more than one caliph at Bagdad about the year 1000 of our present era; the first accurate description satisfying the present-day criteria was that of Fothergill, in 1773.

THERAPY

The Older Analgesics.—None of the sedatives or analgesics is consistently of value in trigeminal neuralgia save only opium, and even it must be given in rapidly increasing doses in order to control the pain; it is therefore used only when trichlorethylene fails and surgical relief cannot be obtained or is refused. It is also stated in the older literature that doses of U.S.P. tincture of aconite sufficient to cause considerable lethargy and a slowing of the pulse to 50 or less, *i.e.*, beginning with 15 minims (1 cc.) three times daily and increasing, will sometimes afford temporary and partial relief.

Trichlorethylene.—This is a strong, sweet-smelling white liquid which was used for industrial purposes in Germany during War I and was accidentally discovered to be of value in relieving trigeminal pain when Plessner presented before the Berlin Medical Society, in 1915, several workers suffering from chronic poisoning by the substance. The present method of administration is to place 20 to 25 drops on a piece of gauze and inhale (lying down because slight dizziness and drowsiness are occasionally caused) until there is no more odor; this three or four times daily for a period of four to six weeks. In those obtaining relief, it is the practice to continue the treatment by inhaling on three consecutive days every two or three months. Glaser (1931), in reporting 15 of his own cases, summarized the results obtained in the 177 reported cases as follows: (*a*) complete relief, about 15 per cent; (*b*) partial relief, from 13.3 to 74 per cent. Later, Horrax and Poppen (1935) stated that of their 90 patients nearly one half obtained sufficient relief that they did not feel obliged to submit to more radical treatment for periods of six months up to six years; in the other patients injection or surgery had to be resorted to very quickly. An advantage of the drug, which would seem to make its trial worth while in any beginning case, is that it does not cause local numbness, as do injection or the surgical procedures. There are many cases of severe poisoning on record as a result of prolonged contact with the drug industrially, but these things need not be feared when it is used therapeutically. However, Eichert's (1937) report indicated the advisability of close surveillance of the patients and frequent checking of the dosage, for he had 2 patients who, as a result of grossly excessive dosage, developed temporary but very alarming mental symptoms.

Typhoid Vaccine.—Schmidt and Sullivan (1939) used typhoid vaccine intravenously at biweekly intervals, starting with a dose of 10,000,000 organisms

and building up with increments of the same or double this size until mild fever responses were obtained. Of their 18 patients, 5 obtained complete relief, 5 over 80 per cent relief; 3 obtained 50 per cent or less and required alcohol injections; in 4 there was complete relief but this was only temporary and injection was required; 1 patient experienced no relief at all and resection was required.

Cobra Venom.—Schmidt and Sullivan (1939) failed to effect relief with this agent in the three cases in which it was tried; Behrmann (1940) succeeded in 1 case and obtained partial success in another.

Alcohol Injection and Surgical Treatment.—The surgical measures available at the present time for the relief of trigeminal neuralgia are: (*a*) alcohol injection of the nerves near the foramina of exit from the skull; (*b*) alcohol injection of the gasserian ganglion; (*c*) the operation of peripheral avulsion of the sensory root; (*d*) radical division of the sensory root; (*e*) an intramedullary tractotomy. All of these measures have their advantages and disadvantages, their advocates and detractors. I believe the selection of the type of treatment to be employed in a given case is so serious a matter that it should not be treated of merely in passing in this book even were I qualified to do so. However, I permit myself to counsel the reader to entrust his patient only to a surgeon who has had much cadaver and actual operative experience in these matters. Injection and surgical procedures are likewise available nowadays for the other rarer types of neuralgia mentioned above.

POSTHERPETIC NEURALGIA

(See *Herpes Zoster*)

SCIATIC NEURALGIA

The majority of the victims of sciatica are males between the ages of thirty and sixty years. In most cases the pain begins in the sciatic notch or in the lower lumbar region and gradually extends down the course of the sciatic nerve. In the beginning this pain is often merely a dull ache that bothers the patient very little, but it finally becomes burning, sticking, or lancinating in character, and radiates downward from the sciatic notch along the posterior aspect of the thigh into the calf muscles and foot. In many chronic cases the pain is ultimately confined to the outer aspect of the calf and foot, where it becomes persistent and causes as much discomfort as the pain in the thigh and buttock during the early stages. Tender spots and areas of paresthesia are frequently noted. Some individuals find the reclining position on the unaffected side, with thigh and leg slightly flexed, absolutely essential for partial comfort, while others, particularly in the later stages, find walking gives greater relief. An attack of sciatic neuralgia may be relatively mild and persist for only a few days, but severe cases are protracted for weeks to months, during which time the patient is entirely incapacitated and suffers severely. Recurrence is the rule.

Pain due to visceral pelvic disease, sacro-iliac strain, arthritis of the lumbar spine and of the lumbosacral and sacro-iliac or hip joint, anatomic anomalies, intervertebral disk lesions, and pelvic and cord tumors must be ruled out in every case of suspected sciatic neuralgia.

THERAPY

Removal of Foci of Infection.—Whatever may be the true cause of sciatica, *i.e.*, whether it be a ganglionitis, a periganglionitis, a neuritis, or an "idiopathic" neuralgia, it is claimed by some men that it is of paramount importance to eliminate all possible foci of infection whenever sciatica is diagnosed. Consequently a huge mound of teeth has piled up outside the jaws of American citizens in recent decades; I wonder how much sciatica has been cured.

Rest, Analgesia and Physical Therapy.—In the early stage of an attack, complete rest in bed and the application of some form of heat along the course of the nerve, especially in the gluteal region, are efficacious measures. If combined with the salicylates as used in the treatment of acute rheumatic fever, the case is often controlled, though it is doubtful if these procedures lessen the total duration of the attack. Codeine sulfate, 1 grain (0.06 Gm.), or even full doses of morphine or dilaudid, must sometimes be used in the beginning of very severe cases. Counterirritants are not beneficial, and massage in the acute stage only aggravates the symptoms. Oftentimes it is helpful to place boards over the springs of the bed and to use a mattress of the pad and not the spring type above them. Buck's extension, with 8 to 10 pounds, may be useful in some cases though the pain is often exaggerated in the beginning. The opposite type of treatment also sometimes succeeds according to Colt (1944): the patient lies on his back, well relaxed, with the knees bent over a large firm pillow and presses firmly on a vertical bedboard with the ball of the foot of the affected side, the ankle being dorsiflexed. It is said that short wave diathermy oftentimes relieves this pain, but Dalton (1944) found that during the acute stage the exertion of reaching the physiotherapy department often more than counteracted the beneficial effect of the treatment.

Some men feel that manipulations of the "osteopathic" type are distinctly helpful in selected cases; it would seem that a good many patients found this out for themselves long ago. Many times, after a patient becomes ambulatory, an especially devised corset or belt is prescribed for him; possibly he is even sometimes helped by the gadget.

In 1943, Hurst of Guy's Hospital, in what he called a "debunking" essay on the treatment of sciatica, took the position that the few patients who do not get well after a month of complete rest in bed are in most instances those who need to be referred to the neurosurgeon who will cure them by removal of the herniated intervertebral disk. But the flood of letters "to the editor" of the British Medical Journal which followed the appearance of his paper indicated that there are not many in the profession who are so willing to make a facile classification of patients into those who need rest and psychotherapy and those who require obligatory surgery.

Injection Treatment.—It is claimed that many severe types of sciatica such as would normally last for many weeks or months if treated only by the above described measures have been reduced in duration to only a few days by injection of physiologic saline solution or oxygen or novocaine.

The technic of the simple saline injection of the nerve in the buttocks was described by Burt (1939) as follows: "The patient lies on his face and a pillow

is placed under the pelvis to raise it slightly. The position of the sciatic nerve is marked with a dab of iodine; this position is most easily obtained by placing the thumb on the ischial tuberosity and the middle finger on the tip of the great trochanter. The tip of the index finger will fall naturally on the nerve as it emerges from the lower border of the piriformis muscle. The exact position is confirmed by detecting the maximum point of tenderness. It is advisable to use a lumbar puncture needle, 10 cm. in length—on entering the nerve sheath the patient will feel a pain shooting down to the foot. Inject 20 cc. of the solution (10 cc. of 1 per cent novocain made up to 100 cc. with physiologic saline solution) very slowly and leaving the needle in position, refill the syringe. Having fixed the syringe in position, slightly withdraw the needle and push upwards into the piriformis muscle and inject a further 50 cc. Even if the saline does not penetrate the sheath of the nerve relief may be obtained."

The technic of oxygen injections was described by Brown (1944), who did not, however, claim originality for it: oxygen is injected from a cylinder via a wash bottle with warm water into the subcutaneous tissue over the sciatic nerve until the surrounding tissues are thoroughly distended and ballooned, when the needle is withdrawn and the process repeated lower down. When the emphysema has disappeared in the course of two or three days the same process is repeated.

Price (1944), who said that he had injected local anesthetics with satisfactory results in about 800 cases, proceeded as follows: the aim is to inject into the foramen where acute tenderness is produced upon deep pressure by means of a probe; the hypodermic needle is inserted to a distance of about 1 inch before making the injection. The treatment is always reinforced by active forcible exercises, and it was stated that determined patients who persevere with the exercises for the rest of their lives do not suffer from recurrences.

Fever Therapy.—Of course with the present vogue of fever therapy, sciatica has also come in for its share of attention; I have seen no report of a series of cases in which it was possible to determine how much of the claimed relief was definitely attributable to the hyperpyrexial bouts. Fever therapy methods are under Syphilis.

MENIERE'S DISEASE

This is a malady characterized by recurring attacks of deafness, tinnitus, nausea and vomiting, and dizziness in which objects rotate or jump rapidly. It is believed that Martin Luther was suffering one of these attacks when he hurled the famous ink-pot at the Devil who was plaguing his ear. Ménière's description established the clinical entity in 1861, but to date all pronouncements regarding its causation are still largely speculative. Atkinson's very interesting hypothesis is that the syndrome results from vasomotor disturbances which are in some instances allergic in nature and possibly migraine equivalents; the Furstenberg diet and its later modifications resulted from reinvestigation of the proposition made some years ago by Danish observers that a waterlogged labyrinth associated with disturbances in salt and water metabolism underlay the syndrome; Talbott and Brown have felt that partial depletion of tissue potassium may underlie the trouble; Dandy seems still to feel that the trouble lies in the eighth nerve itself rather than in the end organ;

Horton and his associates believe that the disturbance consists essentially in localized alteration of the permeability of the capillary walls with resultant edema in the inner ear, the labyrinth being a site most frequently involved with tinnitus and diminution of hearing evidencing secondary cochlear involvement. Practically all of the victims of Ménière's disease are in or past middle life; the left side is more often affected than the right. The onset of the attack is usually very sudden and violent; the patient may be incapacitated for a few seconds, a few hours, or a few days, but between attacks he is usually completely free from symptoms.

THERAPY

Low Sodium-High Potassium.—Furstenberg *et al.* (1934) reported good results with a diet of low sodium content coupled with the intermittent ingestion of ammonium chloride. This treatment not giving great satisfaction in the hands of all workers, Talbott and Brown (1940) proposed the use of a diet of normal sodium content but proportionately higher in potassium. This regimen is very simple since it merely comprises the taking of a normal diet plus 6 to 10 Gm. ($1\frac{1}{2}$ to $2\frac{1}{2}$ drachms) of potassium chloride in aqueous solution daily. (The matter of low sodium-high potassium regimens is discussed fully in Chronic Nephritis.) All except a few of Talbott and Brown's 40 patients were reported sufficiently helped by this regime to be able to live relatively normal lives, but cure was not claimed in any case. Walsh and Adson (1940), not being impressed with the record of the Furstenberg treatment in their 128 patients, also turned to high potassium feeding—using 9 Gm. of potassium nitrate daily instead of the potassium chloride of Talbott and Brown—in conjunction with a low sodium diet. It is not evident from their data that superior results were obtained with this regime.

Low Sodium Diet.—Avoid all of the following: all salt meats and fish and bread, crackers and butter prepared with salt; carrots, clams, condensed milk, raisins, caviar, cowpeas, olives, spinach, cheese, endive, oysters. Take the following no more than twice weekly: lima beans, beets, buttermilk, cantaloupe, cauliflower, celery, chard, dried coconut, dried currants, dates, figs, horseradish, kohlrabi, limes, muskmelons, peanuts, peaches, mustard, pumpkin, radishes, rutabagas, strawberries, turnips, turnip tops, watercress. Of course all food is to be prepared and served without salt.

Histamine.—At the time of the last report which I have seen, Horton (1941), of the Mayo Clinic, had given 1272 intravenous injections of histamine without any untoward effects. Dosage and method: 1 mg. of histamine base is added to 250 cc. of physiological saline solution and this quantity then introduced intravenously during about one and one-half hours (50 to 60 drops per minute). All of Horton's 49 patients obtained prompt relief from vertigo, nausea and vomiting; less than half obtained improvement in tinnitus. Of these patients, 25 had previously undergone some form of Furstenberg treatment (see above) with some degree of palliative effect, "but the fact that they returned to the clinic for additional treatment indicated that they were not satisfied with the improvement. Some had received no benefit." Some patients seem to get along for months with only the one injection or a few such injections in daily succession in the beginning. For maintenance, Horton suggested 0.1 to 0.2 mg. of histamine base subcutaneously two to four times a week, but Rainey's (1943) experience led him to doubt the value of such maintenance dosing. Atkinson (1942) concluded that histamine will not relieve all or even

most cases of Ménière's syndrome. He believed that in most patients the attack is due to a vasoconstrictor mechanism and that in such patients all that histamine can do is possibly to relieve the acute attack through production of powerful peripheral vasodilatation; but he thought that any peripheral vasodilator would do the same thing and has in fact himself recorded cases in which acute attacks were relieved by amyl nitrite and acetylcholine and nicotinic acid (see below). Atkinson further maintained that histamine repeated at regular intervals as maintenance dosage often induces increased frequency and severity of attacks and sometimes an increase in deafness. If I understand Atkinson (1943) correctly he would confine the use of histamine to the small group of patients, less than a fourth of all cases, who are shown to be histamine-sensitive by a cutaneous test; these patients he believes can be treated effectively by gradual desensitization to histamine.

Nicotinic Acid (Niacin).—Atkinson (1943), believing that the vast majority of patients have their attack as the result of vasospasm, obtained improvement in 45 of his 49 cases through the employment of nicotinic acid as a vasodilator. He gave daily intramuscular injections of 25 mg.—building the amount up somewhat slowly if it was necessary—while at the same time giving nicotinic acid from 50 to 100 mg. or more by mouth daily. He said that in some instances patients were able to get on after a while with the oral administration only but others continued to need an occasional injection as well. It will be interesting to see whether anyone else reports equally satisfactory results with nicotinic acid.

Surgery.—It is almost universally conceded, I believe, that Ménière's disease can be permanently cured by division of the auditory nerve. In the hands of a specialist in this procedure the operative risk is exceedingly low; Dandy (1941) reported that he had performed 401 operations, with 1 death—the 358th case—due to meningitis. Grove (1941) felt that surgical intervention should be reserved for patients who have not responded to a medical regime or who for one reason or another cannot be kept on such a regime; he felt that when operation is indicated the differential section of the vestibular portion of the nerve should be the operation of choice for those with usable hearing.

MYASTHENIA GRAVIS

Though occasionally occurring in children and even infants, this is usually a disease of early adult life, the patients being as often women as men. It is characterized outstandingly by excessive fatigability of the muscles, especially those of the face, throat and neck, so that the eyes cannot be opened, there is difficulty in speaking, chewing and swallowing, and the head may roll about loosely. As the disease advances no amount of rest affords sufficient access of strength to break through the paralyses, but actual muscle atrophy is rare and the central nervous system does not really seem to be involved, though the entity is most conveniently studied among the diseases of this system. There are remissions in the course of myasthenia, but ultimately, after months or years, the patient becomes permanently bedridden and dies from exhaustion or pneumonia; in an occasional case, however, the only signs and symptoms are those referable to the ocular apparatus. The etiology of the disease is still

unknown and in its early stages it is not always easily differentiated from neurotic disturbances; the ergograph, prostigmine, quinine and curare tests are, however, valuable diagnostic aids. Wilson and Stoner (1944) have shown that the serum of myasthenia gravis patients produces a block in nerve-muscle transmission which appeared to be due to an alcohol-soluble substance which it contains, and Torda and Wolff (1944) have obtained results suggesting that there is a defect in acetylcholine synthesis in the disease; however, the full significance of neither of these findings is established as yet. Blalock *et al.* (1939) collected from the literature 53 proved instances of myasthenia gravis associated with abnormalities of the thymus this being about one-half the cases of the disease in which postmortem examinations or the findings at operation had been reported. McEachern (1943) said that x-ray evidence of thymic enlargement or tumor is rarely found. Hereditary transmission or familial incidence has not been conclusively shown, though there are some interesting reports such as that of Riley and Frocht (1943), whose two patients were sisters, and Strickroot *et al.* (1942), whose myasthenic patient gave birth to a myasthenic infant.

THERAPY

Educating the Patient.—Some years ago Boothby emphasized the importance of educating the patient. Instruction should include: (*a*) information that in some instances the disease apparently becomes self-limited and that if the patient takes excellent care of himself he may survive into a period of comparative well-being; (*b*) instruction how to conserve strength for eating and swallowing and not to waste it in talking; (*c*) training in the passage of a Rehfuss tube through the nose into the stomach for the administration of fluids and food.

Prostigmine (Neostigmine).—In 1934, Walker reported the successful use of physostigmine in a patient in whom she had tried the drug because of the partial resemblance of myasthenia to mild curare poisoning, physostigmine being known as an antagonist in the latter condition. When prostigmine, an analogue of physostigmine asserted to have less pupil- and accommodation-fixing effect on the eye and less depressing effect on the heart, was introduced shortly thereafter, she also reported the successful use of this drug in a single case. Shortly, Pritchard (1935) and Laurent (1935) each reported effective use in 7 cases, and the wide employment of the drug began. The mechanism of the action is still unexplained, for the assumption that the drug inhibits cholinesterase activity of an excessive degree remains gratuitous since available evidence fails to establish firmly any departure from the normal esterase values in the disease. However, a large number of reports have accumulated to show that prostigmine is very effective in quickly causing partial to complete disappearance of the typical symptoms during a relapse. Viets (1944), of the Massachusetts General Hospital, summarized his experience with the drug in 100 patients, some having been seen throughout an eight-year period and some observed for less than one year. In the 100 cases there were 22 deaths in eight years, which Viets contrasted with the mortality of 70 to 80 per cent which he believed to occur before the introduction of prostigmine into therapy; he also stressed the point that the 22 patients in his series who died were in the later years of life. Particularizing the 45 ambulatory patients seen during 1942–43, Viets stated that about half were maintained on 8 to 14 prostigmine bromide pills a day, each pill being $\frac{1}{4}$ grain (15 mg.). One patient took 20 pills

each day, another 25, the average intake being 10.9 pills each twenty-four hours, or 163.5 mg. of prostigmine bromide. Viets stressed the point, also made by Laurent and Walker (1943), that treatment must be highly individualized and that most patients cannot take enough prostigmine to be optimally maintained. All of these patients with respiratory distress have written instructions from his clinic regarding the use of prostigmine methylsulfate intramuscularly. Three or four of the 45 patients above mentioned resorted to such injections a few times a year, two or three ampules of 0.5 mg. each being used at one time, with or without atropine sulfate. Viets says their tendency at the clinic has been to teach the patient as thoroughly as possible the use and abuse of both forms of prostigmine and allow him to make the ordinary decisions regarding dosage just as one trains the diabetic to use insulin. In their seven-year-old patient, Yahr and Davis (1944) gave a daily dose of 22 mg. orally and 0.75 mg. every other day intramuscularly. In several emergency situations in adults, Viets (1944) has given 1.5 to 3.0 mg. of the methyl sulfate salt intravenously, adding it to dextrose solution and introducing it by the drip method during one hour.

Other Drugs.—Minot *et al.* in 1939 reported useful effects in 5 of 7 patients in whom *guanidine hydrochloride* was given either alone or to supplement prostigmine. They gave the drug either intravenously in 2 per cent solution or orally in capsules, finding 10 mg. a safe and adequate test dose. Total daily dosage and spacing had to be developed in each case individually. Gastrointestinal symptoms seem to serve as a warning that tolerance has been exceeded. In 1941, Dodd *et al.* of the same group of workers stated that of the 21 cases reported to them by other physicians, 4 had been considered markedly benefited by guanidine. In 1935 Laurent and Walker introduced the use of *potassium chloride;* the drug is given in amounts of 20 Gm. in 25 per cent solution by mouth daily. *Ephedrine sulfate* and *benzedrine* (*amphetamine*) *sulfate* have also been used.

Laurent and Walker (1943) said that their prostigmine-treated patients all take some adjuvant drug—guanidine, ephedrine, or potassium salts—and that the prostigmine dosage was undoubtedly reduced in this way. Wilson and Stoner (1944) reported that the addition of 1 grain (60 mg.) of ephedrine sulfate to each prostigmine dose greatly enhanced the action of the latter drug. In Viets' (1944) series, 36 of the patients supplemented prostigmine with 24 mg. doses of ephedrine sulfate, the average being about three doses in twenty-four hours. Other supplementary drugs were less commonly taken and many of the patients finally omitted all of the drugs except prostigmine.

I have heard it said that *testosterone* has been used effectively in 2 cases out of 5 at one clinic, but I have seen no report of this in the literature. *Glycine* (*aminoacetic acid*) has proved entirely unsatisfactory and has been discarded.

Thymectomy.—In 1939, Blalock *et al.* reported the removal of a tumor from the thymic region with greatly improved status for the three years preceding the report. McEachern (1943), reviewing the entire subject of the relationship of the thymus to myasthenia gravis, tabulated the 13 cases in which operation had been performed for the removal of the thymus or of a thymic tumor up to that time. All of the patients who survived operation appeared to show some improvement, in a few instances amounting to cure; but complete disappearance of symptoms did not result in all cases despite apparently complete thymectomy. Later in the year Carson (1943) reviewed the 12 cases studied with Keynes: 3 of the patients died as a result of the operation; 3 recovered

and had remained well nine, six, and three months after operation; 3 had improved. At the same meeting, Brain (1943) said that thymectomy had been performed upon 3 of his patients and had not benefited any of them. More recently Keynes (1944) said that the results of thymectomy are very erratic and that he feels the surgeon is treading on uncertain ground in this field.

X-Ray.—McEachern's (1943) review indicated that no conclusions can be drawn from the few reports of x-ray therapy directed to the thymus in myasthenia gravis that are available.

MIGRAINE

Migraine is the name applied to a certain type of periodic headache that is associated with visual, gastro-intestinal and, to some extent, psychic disturbances. The individual who suffers from this disease is usually made aware of the approach of an attack by several days of malaise, perhaps accompanied by vague or definite gastro-intestinal symptoms; or the attack may come on more suddenly following a period of one or more hours of exceptional well-being; or—and this is not infrequently the case—the patient may recognize a night of more than usually sound and refreshing sleep as a warning signal. In most cases the headache is ushered in by visual disturbances; these may be of the nature of flashes of light, or of wriggling threads of light that pass across the field of vision, or of definite loss of visual acuity, and they may disappear before the onset of the headache or persist for some time after the pain begins. If pain is confined to one side of the head, these visual phenomena are usually observed on the affected side only. The pain itself is most intense, and usually, though by no means always, confined to one side of the head. Occasionally asymmetrical sweating accompanies the headache. During the attack, which lasts from a few hours to several days, the patient is sometimes more depressed or confused than can be easily accounted for by the distraught state induced by the pain. In about 50 per cent of cases, nausea and vomiting occur at the height of the attack. Dunning (1942) reviewed the literature indicating that in a very small number of reported cases persistent sequelae indicating the occurrence of intracranial or extracranial vascular accidents have occurred in migrainous attacks; I think, however, that a great many men might be able to make out a good case for the long arm of coincidence in these instances.

Migraine usually appears in the early decades of life and tends to diminish in frequency and severity, and often to disappear entirely, as senescence approaches; sometimes it disappears at puberty and returns at the climacteric. It often is absent during gestation, and may disappear for a long period after one of the acute infectious diseases. Nothing is known definitely regarding the cause of this strange malady, though the tendency is known to be almost certainly hereditary. The similarity between migraine and the recognized allergic group—hay fever, asthma, urticaria, angioneurotic edema, food allergy, etc.—has caused the suggestion to be made that it is truly a sensitization disease. Some observers have also placed it among the endocrine disturbances as a point of departure in their studies. That migraine and epilepsy are transmitted from generation to generation as an expression of the same underlying factor in the germ plasm has been suggested by some of the observations. The

coexistence of migraine and epilepsy is not significantly high, but momentary seizures much resembling *petit mal* sometimes alternate with and may even replace the migraine attacks as age advances. Riley *et al.* (1935) found that routine laboratory investigations do not supply any information of diagnostic value. Von Storch and Merritt (1935) found no consistent deviations from the normal in spinal fluid pressure. Hunt's (1933) reinvestigation by newer methods of the old idea that migraine has something to do with biliary disturbance forced him to conclude that at least local disease or dysfunction of the gallbladder is not the cause of the attacks. Solomon's (1936) investigation indicated that migraine is not caused by a general sympathetic dysfunction. Schumacher and Wolff's (1941) interesting studies indicated the possibility that the preheadache prodromata follow occlusive vasoconstriction of cerebral arteries whereas the headache itself results from dilation and distention chiefly of branches of the external carotid arteries. The observations of Redisch and Pelzer (1944) during migraine attacks induced by forced water ingestion indicated to them a definite relationship between the fluid balance of the body, the state of the peripheral capillaries and the migraine attack. Atkinson (1943) held that migraine and Ménière's disease may be so related that the one condition can merge into the other. The migrainous headache must be differentiated from headache occurring in hypertension and in nephritis with retention, also from the toxic headache of excessive alcohol and tobacco indulgence, the headache of eyestrain and of nasal sinusitis, the bandlike headache which occurs in some of the psychoneuroses, the headache associated with arthritis of the cervical spine, the headache caused by intracranial lesions and by syphilis, and the headache which Horton differentiates as "histaminic cephalalgia."

Women are the victims of migraine somewhat more often than men, or at least they more often have a severe form of the malady, and the upper social strata are said to be more frequently afflicted than the lower. The variations in racial incidence are not known to me.

THERAPY

Hygienic Measures.—Most patients believe that the smoother and more even the tenor of their life, especially in the particulars of regularity in sleep and the eating of meals, the freer they remain from attacks; some, indeed, are even able to state with positiveness that a certain type of emotional or even physical indulgence will invariably induce the headache. Something of truth there must be in this, but I think its importance is exaggerated by many individuals, for the greatest success in regulating these matters often results in little or no decrease in either frequency or severity of the seizures. The elimination of foci of chronic infection is sometimes rewarded by a remission of many months; but almost invariably the attacks return after a while, though they are oftentimes permanently lessened in severity. Many a migraine patient is addicted to the habit of taking "a brisk saline purge" at the first hint of the prodromata, but I do not think it is apparent that he is much helped thereby.

Rest, Analgesics and Sedatives.—Rest in bed is nearly always self-imposed by the worst sufferers from this disease, since it markedly lessens the throbbing of the head and of course decreases the bodily movements that so often give rise to added quirks of pain. Darkening of the room and the use of cold compresses are also helpful measures. In mild cases, any of the sedative drugs (for a list and dosage, see Insomnia) may be employed, phenobarbital (luminal)

being latterly preferred. In severe attacks, prohibitive doses would have to be used in order to bring about any reduction in the suffering. Better results follow the use of the analgesics in mild cases, though their effectiveness seems to be much greater when the attack is beginning to wear off than when it is at its height. Aspirin (acetylsalicylic acid), in a dose of 5 to 15 grains (0.3–1 Gm.) at intervals of three hours for 4 or 5 doses is often used, but it sometimes serves only to make the patient more uncomfortable by reason of the perspiring induced. A capsule of pyramidon (amidopyrine) and caffeine citrate, 5 grains (0.3 Gm.) of the former and 2 grains (0.13 Gm.) of the latter, three or four times during the twenty-four hours, is effective in some cases; but one should be definitely aware of the danger of inducing agranulocytosis with this drug—personally, I feel that its use is probably no longer justified. Five grains (0.3 Gm.) of phenacetin (acetphenetidin), or 3 grains (0.2 Gm.) of acetanilid, may also prove effective, especially when combined with caffeine as above, if used several times at three-hour intervals; larger doses are seldom more effective and are more likely to cause the undesirable side-effects of this group: sweating and chills, gastric disturbances, skin eruptions, renal irritation, methemoglobin cyanosis and collapse. In some cases, codeine sulfate in a single daily dose of ½ to 1 grain (0.03–0.06 Gm.) is very effectively employed, but is open to the charges applicable to all the opium series: the locking of the bowel and the production of nausea and a general depression in the metabolic activities. Habit formation, in the sense in which the term is understood in connection with the opiates, need not be feared from the use of codeine. Morphine, dilaudid and demerol are, of course, absolutely contraindicated.

Ergotamine Tartrate (Gynergen).—This drug has apparently made a very certain place for itself, though it seems to me not impertinent to remark that a healthy skepticism is still in order, migraine being what it is. The work with ergotamine began on the Continent but a number of American reports are now available; the best of these for presentation here is still probably that of O'Sullivan (1936), who with her associates made a careful study of the drug's effects at Bellevue Hospital. The following are the significant points: (*a*) All but 8 of the 97 patients were benefited in the sense of having obtained great relief from the drug during their attacks but there was no effect upon the frequency of attacks (in a more recent report Trowbridge *et al.*, 1942, obtained relief in about the same proportion of their 48 cases). (*b*) Once the drug has abolished an attack it never fails to do so again if used in adequate dosage. (*c*) It is not necessary to increase the size of doses with the passage of time. (*d*) If the patient takes the drug as soon as she is sure that an attack is on the way the dosage required to check the attack is much smaller than if she delays. (*e*) The time required for effective control varies from fifteen minutes to five hours. (*f*) The drug is preferably given subcutaneously in a trial dose of 0.25 mg.; if the control has not been perfect after two or three hours, the dose is repeated, or it is repeated if the attack returns after eight to twelve hours. In those instances in which repetition is necessary, 0.5 mg. is given initially in subsequent attacks; more than this in any attack is rarely needed, 0.75 mg. having been used only three times. (*g*) It is most important that the patient lie down for one or two hours after medication, not only to assist it but also to diminish the symptoms of overaction of the drug, which occur in many individuals: nausea, vomiting, muscle pains and weakness of the legs, stiffness of joints, a sense of constriction in the throat, and of heaviness in the chest, and burning and tingling of the fingers and toes. A hypodermic injec-

tion of atropine sulfate, 1/100 grain (0.6 mg.), will check the gastro-intestinal distress, and 10 cc. of calcium gluconate solution intravenously diminishes the muscle pains. (*h*) Response to oral administration of the drug in tablet form is much less satisfactory; if nausea and vomiting have already set in it is useless. Five of the 1-mg. tablets have been necessary at one time to check an attack even before the appearance of gastro-intestinal symptoms; with such heroic dosage, no more of the drug should be given for twelve to twenty-four hours. (*i*) Use of ergotamine between attacks in the attempt to prevent their recurrence is felt to be unwarranted in view of the very irregular spacing of the attacks; such a practice is also very expensive and possibly dangerous.

That ergotamine tartrate is capable of causing extremely severe damage to the organism is shown in the following reports: (*a*) In Yater and Cahill's (1936) patient, 19 cc. of the standard gynergen solution was administered in one week for control of pruritus associated with jaundice; the gangrene of ergotism which resulted necessitated amputation of both legs. (*b*) The patient of Gould *et al.* (1937) already had symptoms of peripheral arterial disease when she was given 4 daily ampule doses (a total of 1 mg.) of the drug for relief of pruritus; death a few days later with gangrene of both lower extremities. (*c*) Perlow and Bloch's (1937) patient received 3.5 mg. of the drug within a space of ten days for intolerable pruritus. The resultant threatened gangrene was apparently successfully prevented by the use of papaverine hydrochloride: ½ grain (0.03 Gm.) intravenously or by mouth at intervals varying from four to twenty-four hours during five days. Comfort and Erickson's (1939) 2 patients who had severe reactions had also received the drug in the attempt to control pruritus. Von Storch (1938), in reviewing the literature and reporting his own 189 patients treated for one to five years, said that serious ill effects have not followed the use of the drug when it was employed for the treatment of migraine. Nevertheless he said that treatment should be continued with caution in the presence of marked arteriosclerosis, hepatic or renal disease, vitamin C deficiency and hypersensitivity to the drug; contraindications he stated to be septic states, especially when associated with intravascular foci and obliterative vascular disease, particularly coronary disease. Carter's (1940) patient developed severe substernal distress and auricular fibrillation following an injection of ergotamine; she had apparently had no preceding cardiovascular disturbances, but he was not certain that the diagnosis of migraine was correct.

Oxygen.—In 1940, Alvarez and Mason reported that in about 78 per cent of 100 cases complete or marked relief occurred upon the inhalation of 100 per cent oxygen; but it is worthy of note that in 1943 Alvarez was more conservative, saying "unfortunately it fails to help in a considerable percentage of cases." It would hardly seem likely that oxygen inhalation will soon become feasible for the majority of sufferers from migraine, but it is certainly worth pointing out that this type of treatment is not associated with the annoying side-reactions which so often accompany the use of ergotamine.

Other Measures.—All of the following agents have had a more or less satisfactory chance to show what they could do in relieving or preventing attacks, and all have failed to be consistently effective: histamine, epinephrine, ephedrine, mecholyl, estrogenic substance and pituitary follicle-stimulating substance, pituitrin, amyl nitrite, calcium gluconate, trichlorethylene, cannabis indica. Among more recently proposed agents, any one of which may be worth a trial (see index for methods of employment) are: benzedrine (amphetamine)

sulfate, prostigmine, potassium thiocyanate, calcium lactate and potassium chloride concomitantly employed, and urea.

Those who approach the migraine problem from the allergy standpoint are reporting a certain degree of success through employment of the various methods of specific desensitization and especially through the use of nonspecific protein therapy and the employment of measures for the diagnosis and treatment of food allergy. It is suggested that the reader study the chapter on allergy.

The possibility of obtaining relief through inducing menopause has been considered by Alvarez (1940), who found that in only 6 out of 42 cases did oophorectomy or hysterectomy, complete or partial, or a sterilizing dose of roentgen rays or radium put a stop to attacks of migraine; in 5 cases the attacks were milder, in 16 they went on unchanged or were better for only a while and in 15 they became worse.

IDIOPATHIC EPILEPSY

(*Paroxysmal Cerebral Dysrhythmia*)

Idiopathic or essential epilepsy is a disease characterized by a peculiar type of convulsive seizure and a tendency to mental deterioration. It occurs in individuals with a constitutional inferiority but with no demonstrable pathologic lesion and no physical signs or findings which are characteristic of the disease. In the majority of instances the onset of the attacks occurs before the twentieth year, in more than half before the fifteenth, and perhaps in average cases between the third and eighth year; but the time of appearance of the subsequent dementia is very variable. In many cases the imminence of a convulsion is heralded by a warning visual, auditory, or other type of fleeting aura, which is followed, in about 50 per cent of cases, by the sinister epileptic outcry; then follow the sudden loss of consciousness, the defenseless fall, and the moment of pallor, cessation of respiration and general muscular rigidity of the decerebrate type. Transition into the clonic stage, in which the body jerks rhythmically and violently, may be made suddenly and generally or in a disorderly manner, so that one side remains rigid while the other is already jerking. During this stage, which lasts from three to five minutes and subsides slowly, the skin is cyanosed, the pulse is rapid and feeble, the deep reflexes are greatly diminished, the blood pressure is low, the pupils are first constricted and then dilated and usually immobile to light, foam appears on the lips, bestial sounds are made and the urine or feces may be violently ejected. Following the subsidence of this stage, the patient passes into a deep stupor of several hours, though in some instances this stuporous state is not marked or the patient may partially regain consciousness for a few moments and then fall into a more natural type of deep sleep. For a considerable time after awaking, the state is either one of dreaminess, irritability, delirium, or mania during which acts of great violence may be committed. This is the classic *grand mal seizure;* the *petit mal* attack consists in only a momentary loss of consciousness, or some other sort of flashing sensory disturbance, without the occurrence of a convulsion and its sequelae. And then there are the cases in which so-called *equivalents* replace a typical convulsive seizure: unexplained outbursts of temper, tantrums, periods of amnesia, sudden irrational and destructive

activity, periods of dulness and apathy. The *status epilepticus* is a state of affairs in which one convulsion succeeds another so rapidly that the patient practically never recovers consciousness; he presents all the signs of profound intoxication and usually dies from heart failure or pulmonary edema. In rare instances only one or two or three attacks, with many years between, are experienced throughout a long lifetime; evidence is accumulating to show, however, that in most cases of epilepsy the seizures follow various rhythmic patterns too complex for analysis here.

Between attacks the epileptic is likely to be a disagreeable antisocial psychopath, who is gloomy, irritable, suspicious, defensive, boastful and deceitful, to cover his emotional poverty, violent, self-centered and uncomprehending. At all times the person with a severe case of this disease is a dangerous individual; those more mildly afflicted as to number and severity of fits, particularly if the symptoms do not appear until well on toward or into adulthood, suffer very much less mental deterioration—indeed, Barnes and Fetterman (1938) felt that the personality problems of the epileptic are often due to the social and psychologic reactions to his disease rather to any change in intelligence. Paskind and Brown (1943) expressed the feeling that eventual mental deterioration is taken entirely too much for granted in all cases merely because it frequently occurs in advanced committed cases, and they thought that the disorder is definitely of two types: one in which mental deterioration occurs and the other in which it does not. Lennox (1943) stated that at most only one third of adult epileptics are unfit for productive activity.

Epilepsy was recognized as an entity in very ancient times. Sudhoff interpreted the concept *bennu*, in the tablets of King Assurbanipal of Assyria (668–626 B.C.), as epilepsy, and the description of the disease written by Hippocrates (460–370 B.C.) would almost suffice for any present-day textbook. In the Middle Ages it was customary to include epilepsy with the diseases then recognized to be contagious—bubonic plague, tuberculosis, anthrax, scabies, erysipelas, trachoma and leprosy—and to ban the afflicted from the cities, or at least not to permit them to sell food and drink. At the present time we are convinced that the disease is not infectious, and certain that the epileptic predisposition is inherited—it has been said that the chances of transmission of epilepsy by the epileptic are five times greater than by the nonepileptic; but otherwise the etiology remains unknown and a satisfactory classification of the various types is still to be proposed. The claims of those who argue for the inclusion of epilepsy among the diseases of allergy are interesting; Harris has shown that some cases of pseudo-epilepsy are associated with a state of hypoglycemia; in a very small proportion of the cases some demonstrable brain lesion is the sole cause of the seizures; now and then seizures occur as a part of a frank endocrinopathy; undoubtedly cysticercosis of the brain is responsible for numerous cases in the Far East. But the most significant advance in the knowledge of idiopathic epilepsy that has been made in all its long history is the recent recognition, largely as a result of the studies of Lennox and his associates at Harvard, that in about 95 per cent of patients there are abnormalities in the electro-encephalogram which show up even during an asymptomatic period; this is the evidence, indicating that seizures are accompanied by profound alterations in the rate and force of the electrical pulsations of the cortex, which warrants us in applying to epilepsy the new title "paroxysmal cerebral dysrhythmia." It is estimated that about one half of 1 per cent of the inhabitants of the United States suffer from epilepsy.

THERAPY

Hygienic Measures.—If essential epilepsy is incurable, and it probably is in the present stage of our knowledge, nevertheless very much can be done for these sufferers. But the physician who merely writes a prescription for one of the anticonvulsant drugs, makes a few vague remarks as to dietary restrictions, suggests that the family make life easy for the patient, and then takes no vigorous and persistent subsequent steps to see that these measures are instituted to the fullest advantage of the patient, is shirking his bounden duty, for no individual is more prone to suit a treatment to his own convenience or whims, and finally to stop it altogether, than the epileptic.

It is probably true that the rehabilitation of the patient's hygiene, by which I mean his readjustment to his environment, is the single most important element in the treatment. These individuals are defectively equipped to cope with a social existence, and therefore must be especially protected. Fatigue is their greatest enemy, fatigue of mind, body, or emotions; therefore they must be placed in such surroundings that they may perform light work (preferably remunerative so long as their mentality is alert to the significant facts of their plight), be much out of doors, bathe often and keep the skin in good condition, eat nourishing food but not much at a time, have alcohol, tobacco, and to a large extent tea and coffee, withheld from them, and be encouraged not by maudlin sympathy but by a rational optimism to enjoy the many advantages of life that may be theirs despite their handicap. For most epileptics, of whatever station in life, these desiderata can perhaps be best approximated in either a public or private institution, provided it is well conducted; but in many cases the readjustment is better accomplished without too radical a change in environment. Certain it is that to stop at once the education of a child or youth as soon as the diagnosis is made is not justified unless the case be hopelessly severe from the beginning, for many of these children are precocious and will absorb much in their early years that will help to sustain them at a later time; furthermore, no one can predict with certainty that a mild case may not continue to be so always under proper care.

Phenobarbital.—This drug almost completely replaced the bromides a number of years ago but it is now fighting to hold its place against dilantin at least in the treatment of adult epilepsy. Peterman (1942) said that adequate dosage was about $\frac{1}{4}$ grain (15 mg.) two or three times a day for a child under two years of age, $\frac{1}{2}$ grain (30 mg.) at the same intervals from two to six years, 1 grain (60 mg.) from six to ten years of age, and $1\frac{1}{2}$ grains (100 mg.) from ten to fifteen years of age. In resistant cases in adults, $2\frac{1}{2}$ grains (0.2 Gm.) may be given three or rarely four times daily for a limited period, but many adults need no more than $1\frac{1}{2}$ or 2 grains (0.1 or 0.13 Gm.) daily. Lennox (1940) pointed out that $\frac{1}{4}$-grain tablets cost five times as much as $1\frac{1}{2}$-grain tablets; it should be known to everyone by this time that phenobarbital bought under the trade name of "luminal" is more expensive than the official drug. The elixir of phenobarbital of the U.S.P. XII contains $\frac{1}{4}$ grain (15 mg.) in a teaspoonful (actually in 4 cc.).

The soluble phenobarbital sodium is used when it is necessary to administer the drug hypodermically. It is customary to prepare a 20 per cent solution in boiled and cooled distilled water; 15 minims (1 cc.) of this solution contain 3 grains (0.2 Gm.) of the drug. The dose of phenobarbital sodium is 10 per cent greater than that of phenobarbital.

Sudden cessation of phenobarbital administration is almost always followed

by an increase in the incidence and severity of the attacks above that reached before the drug had been started.

The following by-effects of phenobarbital administration are infrequent but should always be borne in mind as possibilities, since they probably occur as often following small as large doses: (*a*) a dermatitis resembling that of measles or scarlet fever, though it is usually very itchy (a few cases of fatal exfoliative dermatitis are on record); Peterman (1931) reported an eruption exactly simulating bromoderma which followed a healed true bromoderma on the same sites; (*b*) a peculiar eruption upon the tongue; (*c*) states of apathy, mental sluggishness and slow speech much resembling those seen as a result of bromide therapy; (*d*) great muscular weakness; (*e*) extreme irritability, sometimes leading to violence; (*f*) a state of intoxication that may be mistaken for acute alcoholism; (*g*) and occasionally subacute and chronic epigastric pains.

None of the other barbiturates has been nearly so effective as phenobarbital in the treatment of epilepsy, but it is much more effective in *grand mal* than in *petit mal*. Southerland (1940) reported a group of institutionalized patients who had fewer seizures when given 1 grain of phenobarbital in the morning and 30 grains of bromide in the afternoon than when given 1 grain of phenobarbital alone twice daily. A number of observers have found it advisable under some circumstances to combine dilantin with phenobarbital (see Dilantin). Cohen *et al.* (1940) reported the elimination of some of the undesirable sedative action of phenobarbital by the concomitant use of 5 to 25 mg. of benzedrine (amphetamine) sulfate daily, but Stone *et al.* (1940) were unable to confirm this finding. Loscalzo (1938) asserted that belladonna alkaloids can replace a part of the phenobarbital, but I have seen no confirmation of his findings.

Just how long the patient may take phenobarbital without being harmed is not known, but Somerfeld-Ziskind and Ziskind's study of 100 noninstitutionalized patients indicated that as much as $1\frac{1}{2}$ grains (0.1 Gm.) two or three times daily may be taken for at least two years (the length of their study) without resultant deterioration of the intellect.

Dilantin (Epanutin).—Since 1938, when Merritt and Putnam, at Harvard, introduced dilantin it has had extensive trial. The drug, which is diphenylhydantoin sodium, is analogous to the barbiturates in its chemical nature, being a derivative of glycolyl urea instead of malonyl urea. In Merritt and Putnam's 1940 report on 267 patients refractory to other forms of therapy (principally phenobarbital) they found the drug effective in reducing or controlling convulsive seizures in 227 instances over periods varying from two months to two years. Greatest effectiveness was obtained in psychic equivalent attacks, next in *grand mal* and least in *petit mal;* the effect upon psychic equivalent attacks is particularly noteworthy because neither phenobarbital nor bromides have much influence upon this type of epilepsy. The findings of the Harvard group have been substantially confirmed by a number of workers. In addition to what appears to be a somewhat greater ability to reduce the incidence of seizures than is possessed by phenobarbital, dilantin has the great advantage of not acting as a sedative; in fact it is the general impression that many patients are mentally brighter while taking the drug. Ross and Jackson's (1940) exact study of this latter point did not reveal any significant influence on intelligence ratings, but about half their patients showed an improvement in conduct, and performance ratings were raised appreciably in a small percentage; McLendon (1943) found that his institutionalized patients with men-

tal deterioration became more friendly and alert under dilantin and required less supervision than was necessary under phenobarbital.

On the credit side, therefore, the record is very fine: probably greater efficacy against *grand mal* than phenobarbital; certainly greater efficacy against psychic equivalents; lack of stupefying or even sedative properties; and possibly an alteration in the epileptic temperament toward the better in some instances. Unfortunately, however, as in all matters in this best of possible worlds, there is another side to the picture. For one thing the drug is more expensive than phenobarbital, and this is a serious drawback to its general use. Another thing is that *petit mal* attacks are often more frequent under dilantin (Lennox, 1940). Then there is the matter of the drug's toxicity. Pratt (1939) reported toxic reactions in 73 per cent of 52 patients, the most frequent in occurrence being subjective tremulousness with a feeling of apprehension and tension, tremors, dizziness, ataxia, nausea and sometimes vomiting, burning sensation in the eyes, diplopia and blurring of vision; psychotic reactions occurred in 5 cases. Williams (1939) found that toxic symptoms arose in 36 per cent of his 83 patients, Blair (1940) in 58 per cent of his 36 patients, and all of Finkelman and Arieff's (1942) 41 patients showed some side effects on the nervous system ranging from apprehensiveness and irritability to a paranoid confusional psychosis and encephalopathy. Kimball and Horan (1939) found peculiar hyperplastic reactions in the gums in about half their patients and so have numerous other observers since; Merritt and Foster (1940) confirmed in man Gruhzit's earlier finding in animals that this gum reaction is not caused by drug-induced vitamin C deficiency, though at times the appearance of the gums does bear some superficial resemblance to the picture seen in scurvy. Less frequently occurring reactions involve the gastro-intestinal tract and the skin (Ritchie and Kolb, 1942, reported a fatal case of hemorrhagic erythema multiforme and there have been a few recorded instances of exfoliative dermatitis); hirsutism in adolescent girls, nosebleed, purpura, cardiovascular disturbances (Finkelman and Arieff, 1942, recorded electrocardiographic evidence of involvement of the heart). McCartan and Carson (1939) reported a slight progressive diminution of the red cell count in all of their 20 patients, a tendency to lowering of the white count due to a fall of granulocytes, and an increase in the number of eosinophils in 13 of the cases; but Merritt and Putnam (1939) did not find such evidences of action on the bone marrow.

Peterman informed me, early in 1945, that he has found dilantin quite unsatisfactory in children and that almost all of the patients whom he has treated with it have returned to phenobarbital by their own choice. As a matter of fact most men find that even in the treatment of adults dilantin is best employed in combination with phenobarbital. Of course the proper dosage combination must be developed through careful trials in each case. The danger to life from the accidental taking of a large overdose of dilantin seems to be very slight: Aring and Rosenbaum (1941) reported a patient who upon four occasions ingested 60, 90, 105 and 57 grains (4, 6, 6.8 and 3.8 Gm.), respectively; the chief symptoms each time were exhilaration, light-headedness, dizziness, nausea and vomiting, headache, staggering diplopia-nystagmus, difficulty in converging the eyes, pupillary abnormalities, ataxia, tremor and changes in reflexes. Robinson's (1940) patient, who ingested 67½ grains (4.5 Gm.), was in coma for a few hours and then suddenly regained complete consciousness.

Dosage.—Merritt and Putnam, whose use of the drug has set the standard, find regulation of the dosage not difficult in patients who are having several or many attacks weekly; 1½ grains (0.1 Gm.) are given in capsule form, preferably with or after meals, three times daily and increased if necessary in increments of 1½ grains (0.1 Gm.) every ten days or two weeks until relief is obtained or toxic symptoms appear; in most cases after the control level is reached this must be maintained without reduction. Patients who have relatively infrequent attacks are often more difficult to treat but they are frequently given 6 to 7½ grains (0.4 to 0.5 Gm.) daily in the attempt to prevent attacks which might interfere with their occupation or education. All observers agree that the change over from phenobarbital to dilantin must be made with extreme caution. Fetterman's (1940) method will serve as an example, it being a scheme which depends on the gradual reduction of phenobarbital over a period of three to four or five weeks with the simultaneous replacement by dilantin in gradually increasing amounts: "If a patient has been receiving, let us say, three tablets of phenobarbital daily, it is a good rule to replace one tablet by one capsule of dilantin sodium daily during the first week and then, during the second week, to replace two of the phenobarbital doses by two capsules of the other drug. During the third week, if there are no attacks, one may replace the phenobarbital entirely, but it is safer to continue with at least one dose of phenobarbital plus three capsules of dilantin sodium. Should attacks continue and no complex side actions develop, the dose of dilantin may be increased to four or five capsules daily for an adult."

The Bromides.—The bromide salts were introduced into the treatment of epilepsy in 1853 and enjoyed an undisturbed and deserved preference over all other remedies until their position was challenged by phenobarbital and more recently dilantin. Bromides have now been almost abandoned but it is well to bear in mind that this abandonment has not occurred because they were not effective. As a matter of fact there are not available any fully controlled large-scale studies of these drugs under the conditions in which the general practitioner employs them, *i.e.*, in the attempt to keep moderately afflicted epileptics economically productive and socially adjusted. Perhaps the nearest approach to such a desirable study was that of Lennox (1940), who tabulated the results in 766 extramural patients who had taken phenobarbital and 289 who had taken bromides. Of the phenobarbital group 65 per cent reported improvement and of the bromide group 53 per cent; improvement in mentality was reported by 30 and 26 per cent respectively. These differences are not of statistical significance considering the great disparity in numbers of patients in the two groups. I am not wishing to make out a case for the superiority of the bromides to phenobarbital or dilantin or even contending that they are probably quite as good, but I think that from the standpoint of accuracy it should be stated that there were other reasons than ineffectiveness for turning away from them when opportunity presented. These reasons are that the bromides not infrequently obtain their good effect at the price of sluggishness and apathy; that the skin rashes often induced by them, if not serious in themselves, are an added embarrassment to an individual already prodigiously handicapped; they often cause gastric disturbances; and they are more expensive than phenobarbital. As is the case with the other drugs also, *grand mal* is more effectively treated by the bromides than is *petit mal.*

There is a firmly entrenched clinical impression that mixtures of several bromide salts are superior to any one alone, so the "Erlenmeyer mixture" (1

part each of potassium and ammonium bromide and 2 parts of sodium bromide) has been much used, as also the elixir of three bromides of the National Formulary, which is a colored and flavored preparation containing in 1 fluid-drachm 5 grains (0.3 Gm.) each of sodium, potassium and ammonium bromide. It is highly probable that full anticonvulsant action can be obtained with either sodium or potassium bromide alone. Average adult dosage is 15 grains (1 Gm.) three times daily but careful study is required to determine, by adjustment up or down from this dosage, the amount required in a given case. Dosage is reduced for children roughly in proportion to their weight. Bromide therapy is more effective if the diet is kept relatively salt-free, but resort to this measure is usually necessary only in very resistant cases.

The following prescription is acceptable for disguising the bromide taste:

℞	Sodium bromide	℥i	30.0
	Water	℥i	30.0
	Syrup of glycyrrhiza to make	℥iv	120.0

Label: 1 teaspoonful in water or milk three times daily.
(Note: 1 teaspoonful = 15 grains, 1 Gm. of sodium bromide)

Bromide overdosage is evidenced by foul breath and coated tongue, any one of the characteristic skin lesions especially sudden and extensive acne, lethargy and mental dulness, slurring of speech, slow pulse and a staggering gait. Treatment consists in stopping the administration of the bromide and in pushing fluids and giving sodium chloride. Sensenbach (1944) stated that the giving of 6 to 8 Gm. of sodium chloride daily appears to be optimum dosage, but he warned that the response to therapy is slow and rarely dramatic and that the blood bromide level always falls before there is any appreciable change in the patient's mental state. Toenhart (1935), confirmed by others, showed that continuous aspiration of the stomach materially hastens bromide elimination; under these circumstances saline should be administered intravenously. The reported successful employment of adrenal cortical extract is not likely to stand the test of time as it seems to be scientifically unsound; indeed it has already been soundly criticized for this reason and also on the basis of actual failure to confirm the clinical findings.

Glutamic Acid.—Price *et al.* (1943) initiated a clinical experiment employing *dl*-glutamic acid hydrochloride in the treatment of epilepsy, principally, it seems, because it is the only amino acid known to be metabolized by slices of brain tissue. I mention the matter here only because when other anticonvulsant therapy was continued the addition of this glutamic acid effectively reduced the incidence of *petit mal* and psychomotor attacks and increased mental and physical alertness in the small number of patients in which it was tried. This new departure will certainly be watched with a great deal of interest.

The Ketogenic Diet.—Fasting as a dietary measure in the treatment of epilepsy was first suggested by Guelpa and Marie, in 1910, but it was not until 1921 that Geyelin applied the suggestion in practice. Most of his children were freed from seizures during the period of fasting which produced ketosis, but the attacks returned sooner or later after the resumption of a normal diet. Repeated periods of fasting were thus shown to be impractical in the maintenance of ketosis. However, in the same year Wilder, while working with high-fat diets in the treatment of diabetes mellitus, suggested their use in the treatment of epilepsy as a means of producing ketosis and still supplying adequate food. This marked the beginning of the ketogenic diet, so called because the ketogenic factors outbalance the antiketogenic factors; but evi-

dence has been accumulating to the effect that it is not the disturbance in the acid-base balance *per se* (*i.e.*, not any sort of sedative, anticonvulsant effect of the ketone bodies) but rather the dehydrating effect of starvation, or of a ketogenic diet, which is important in bringing symptomatic relief—an idea originally suggested by both McQuarrie and Fay in 1929. The hypothesis is that in epilepsy there is an increased production of cerebrospinal fluid in the nonextensible cerebrospinal space, that this increased pressure is associated with the convulsions in some causative or provocative relation, and that the effect of the treatment is the result of the removal of this surplus of extracellular fluid. Clinical attempts to test the hypothesis by simple reduction of the allowed fluids to a very low point were not productive of satisfactory results in the hands of Fetterman and Kumin (1933), and Wilson and Limberger (1933). The study of Greville and Jones (1940) seemed to reveal that retention of body water does not by any means invariably precede a seizure; however, Ziskind *et al.* (1939) were often able to precipitate seizures by the administration of excessive quantities of water, a procedure which is sometimes employed as a diagnostic aid. Despite the conflicting evidence a number of men believe that dehydration is of value in conjunction with both drug therapy and the ketogenic diet.

The new method of attack upon this ancient enemy was grasped with avidity by the pediatricians, so that the earliest reports were of its results in the treatment of children. In 1932, Peterman, of Milwaukee, reported a series of 85 patients, 42.5 per cent of whom had been free of convulsions for from six months to three and one-half years; of the 267 children in whom adequate trial of the diet was made at the Mayo Clinic since 1922, Helmholz and Goldstein (1937) reported that 31 per cent were freed from attacks for at least one year. In both series, as in the experience of other observers, a considerable number of patients was much helped but not completely relieved of attacks—Amoss (1938), indeed, reported a case in which the diet increased the number of the seizures and also their duration and severity. Wilkins (1937), at Johns Hopkins, felt unable to evaluate scientifically the results obtained with the diet but believed the successes sometimes had in cases of a type most unresponsive to other therapeutic measures justify its trial whenever attacks are not controlled by sedatives. Logan and Baldes (1942), of the Mayo Clinic, found that in 267 children freedom from attacks was obtained in 31 per cent and definite improvement in an additional 16 per cent. McQuarrie (1942) stated the belief that the ketogenic diet remains the most effective treatment for epilepsy in children and the only treatment which has any effect on *petit mal;* Peterman (1945) is in agreement. In his selection of patients, the latter author excludes all with any evidence of organic lesions and those who are already sufficiently advanced in the disease to have reached the stage of mental deterioration.

In 1930 Barborka, who had carried the diet over into the treatment of adults, reported complete control of attacks in 12 per cent of 100 patients, though again, as in children, considerably more than this proportion obtained some help. Observers are agreed that upon the whole the treatment is much less effective in adults than in children.

Diet for Children.—After a preliminary fast of ten to fourteen days, with the patient in bed, during which the daily allowance is only 6½ ounces (200 cc.) orange juice, 13 ounces (400 cc.) diabetic broth, bran wafers as desired and 13 ounces (400 cc.) water, the ketogenic diet is begun abruptly. For the general practitioner who has not an expert dietitian at his elbow, it seems to me that

the best that can be done is to follow the general plan recommended by Peterman: (*a*) a definite daily regimen to include a long nap and a long sleep, meals at regular hours and a daily bowel movement; (*b*) restricted carbohydrate and protein and a high-fat diet; (*c*) fluid restriction to a minimum, at least to 600 or 800 cc. daily and less if convulsions continue; (*d*) phenobarbital in large enough doses to control any seizures which may occur after or until the above procedures are established.

He offers the following sample menus for a child of five years, who is to receive daily 15 Gm. C, 18 Gm. P, and 132 Gm. F, and for a child of ten years, who is to receive daily 15 Gm. C, 34 Gm. P, and 177 Gm. F:

SUGGESTED KETOGENIC MENUS FOR CHILDREN

Five Years of Age

Breakfast

30 Gm. sliced orange
13 Gm. butter
1 egg—omelet
100 Gm. 30 per cent cream
May have "Cellu" bran breakfast food

Dinner

30 Gm. spinach
10 Gm. butter
20 Gm. scraped beef pattie
50 Gm. cream for drinking
50 Gm. cream—ice cream { Whip cream and flavor with ¼ teaspoonful vanilla, ½ gr. saccharin
May have bran wafers

Supper

Celery soup { 50 Gm. cream, 20 Gm. celery, 10 Gm. butter
50 Gm. asparagus
6 Gm. butter
50 Gm. cream
May have "D.Zerta"
Fluids—300 Gm.
1000 cc. − 300 cc. = 700 cc. water may be allowed between meals.

Ten Years of Age

Breakfast

30 Gm. fresh pineapple
20 Gm. butter
1 egg—scramble with cream and butter
100 Gm. 30 per cent cream
May have "Cellu" bran breakfast food

Dinner

50 Gm. broiled tomato
20 Gm. butter
70 Gm. steak with mushrooms (no available food value in mushrooms)
75 Gm. cream to drink
1 "D.Zerta" with 25 Gm. whipped cream

Supper

Vegetable soup { 50 Gm. broth, 10 Gm. celery, 3 Gm. onion, 4 Gm. carrot, 20 Gm. butter { 20 Gm. 3% veg.
20 Gm. raw cabbage with 12 Gm. mayonnaise
20 Gm. bacon
100 Gm. cream—cocoa { 100 Gm. cream, ¼ tsp. cocoa, ½ gr. saccharin
Fluids—350 Gm.
1000 cc. − 350 = 650 cc. water may be allowed between meals.

When the diet is found that will keep the patient free from seizures, which may require increasing the fat to the point of intolerance, it should be maintained four months, then additions of protein, 10 Gm., are made every two months alternating with additions of carbohydrate of the same amount.

Diet for Adults.—Most adults cannot be made to stay on this diet, which would not surprise any physician if he tried it for a short time himself. Clark (1936) offered the following simplified menu, with the supplementary instructions that (*a*) saccharin may be used for sweetening; (*b*) there should be no gum chewing, tobacco, cathartics other than liquid petrolatum or bitter cascara, no medicines not prescribed; (*c*) bran wafers must have no food value; (*d*) water is allowed in only very moderate amounts; (*e*) if nauseated omit a meal or two, taking one-half glass of tomato juice, one-half orange or a glass of sour lemonade.

SUGGESTED HIGH FAT KETOGENIC DIET FOR ADULTS (Modified from Clark)

Menu Plan

Include the following foods daily, in the exact amounts specified:

Heavy whipping cream	1½ pints (3 cups)
Eggs	6

Any combination of 2 eggs and 1 cup of cream may be used at each meal. Below are three suggestions. If desired, some cream may be used between meals with coffee or tea.

Breakfast:

Scrambled eggs	
Eggs	2
Heavy whipping cream	¾ cup
Bran wafers	as desired
Heavy whipping cream	¼ cup
Butter	as desired
Coffee or tea	as desired

Lunch:

Poached egg	1
Baked custard or custard ice cream	
Egg	1
Heavy whipping cream	1 cup
Water	¼ cup
Nutmeg and saccharin	if desired
Bran wafers	as desired
Butter	as desired

Dinner:

Egg omelet	
Eggs	2
Heavy whipping cream	½ cup
Bran wafers	as desired
Iced coffee	
Coffee	as desired
Heavy whipping cream	½ cup
Butter	as desired

Nesbit and McDonnell's (1935) type of diet was a clever one; instead of supplying excess fat in a maintenance diet they simply supplied a diet so much below maintenance requirements that the patient achieved ketosis through utilization of his own body fat. The diet was successful in a large number of patients, though ketosis is necessarily slowly achieved with it; patients did not find it nearly so repugnant as the other type of diet.

SUGGESTED LOW-CALORIE, LOW-FAT KETOGENIC DIET FOR ADULTS

(Nesbit and McDonnell)

Breakfast

Egg, 1
Bacon, 2 long strips
Cream or milk, 1 tablespoonful
5 per cent vegetable, ½ cup cooked
Bran wafers as desired*
Butter as desired
Tea or coffee

Luncheon

2 eggs or 2 ounces of meat or fish or 3 tablespoonfuls of cottage cheese
5 per cent vegetable, ⅓ cup cooked or ½ cup raw, or 5 per cent fruit
Cream or milk, 1 tablespoonful
Bran wafers as desired*
Butter or mayonnaise as desired
Tea or coffee

Dinner the same as luncheon

* Bran wafers must have no food value.

Sample Menus for Day

Breakfast	*Luncheon*
1 egg fried with 2 strips of bacon	Cottage cheese, 3 tablespoonfuls
½ cup of tomato juice	⅓ head lettuce with 2 tablespoonfuls of mayonnaise
Bran wafer with butter	Bran wafers with butter
Coffee with 1 tablespoonful of cream	Coffee or tea with 1 tablespoonful of cream

Dinner

Steak, 2 ounces
Cooked spinach, ¼ cup with butter
Raw celery, 2 stalks
Bran wafer with butter
Coffee or tea with 1 tablespoonful of cream

No sugar is allowed. Chewing gum, chewing tobacco, toothpaste, sweetened cathartics and the like are not allowed. Gluside (saccharin) may be used for sweetening. Fruits must be fresh or canned without sugar. Mayonnaise should be made without sugar.

Treatment of the Attack.—In a few individuals with a long aura, the use of amyl nitrite, by inhalation from a pearl crushed in the handkerchief, will sometimes abort an attack. During the course of a seizure about the only thing that can be done is to prevent injury insofar as is possible. A spoon or other object should be introduced between the teeth to prevent biting of the tongue, the clothing should be loosened, the mucus removed from the mouth, and the site of such gross injuries as may have been received in the fall protected as much as possible during the clonic period. Nocturnal epileptic attacks often precipitate the patient out of bed unless special safeguards are provided. The promotion of a quick return to consciousness by the use of cerebral stimulants is contraindicated, for such forced recovery from stupor is often obtained at the price of a terrific headache and very prolonged exhaustion.

Treatment of Status Epilepticus.—The most usual methods of treating this state are by the use of strong purges, colonic irrigations with cold water, applications of ice to the spine, large doses of bromides, chloral hydrate, morphine, or dilaudid, paraldehyde, phenobarbital sodium and chloroform. Bromides must be used in a large dose of 60 to 80 grains (4–5.3 Gm.), or chloral hydrate may be given in the same amount by rectum; morphine or dilaudid in full dose is sometimes combined with either of these drugs. Grinker (1929) gave 3 to 5 grains (0.2–0.3 Gm.) of phenobarbital sodium intraspinally in 5 to 10 cc. of physiologic saline after drainage; intravenous injections of 3 grains (0.2 Gm.) every four hours may be made. Collier (1928) preferred paraldehyde to any other remedy, giving it in a dose up to 8 drachms (32 cc.) in an equal quantity of olive oil by rectum; Wechsler (1940) found 1 cc. of the drug injected intravenously the most effective agent he had ever used. When a general anesthetic is necessary, chloroform is preferred to ether because of its quicker action. Robinson's careful studies at the New Jersey State Village for Epileptics convinced him that chloroform, pushed only to the point of producing complete relaxation, is the best remedy of all. Venesection should probably never be practiced unless injection of physiologic saline is made at the same time.

During the postconvulsive stupor, it may be necessary to continue the use of anticonvulsants, for these patients are often in a state of motor unrest even after the convulsions have ceased. Supportive treatment is most important: alcohol, digitalis, caffeine, as indicated. The use of nutritive enemata and fluids by hypodermoclysis or intravenously may be necessary, bearing in mind the great metabolic upheaval that has been experienced by the body. Delirium is

perhaps best controlled by scopolamine hydrobromide, 1/200 to 1/100 grain (0.3–0.6 mg.).

Storchheim (1933), feeling that pulmonary edema with consequent or accompanying heart failure was largely responsible for the fatal termination in his 5 patients treated with sedatives or anesthetics, turned to the intravenous injection of magnesium sulfate. He gave 10 cc. of a 25 per cent solution, very slowly and between convulsions, to an adult, repeating once or twice if necessary. In 1937, shortly before his untimely death, Storchheim kindly informed me that 20 patients had been treated, all successfully; 1 patient had been brought through 30 attacks of severe status with no more mental deterioration than when first seen five years previously. But Peterman and Glaser (1944) lost a case in which the agents, including magnesium sulfate, were used in large dosage and without effect in the following order: phenobarbital, dilantin, magnesium sulfate, calcium gluconate, divinyl ether, amytal, chloral hydrate, ether, codeine, chloroform, avertin, scopolamine and paraldehyde.

INSOMNIA

We have no reliable gauge of the optimum amount of sleep for the adult human, though it almost certainly varies widely with individuals, nor have experimental studies shown convincingly that moderate periods of enforced wakefulness in the healthy are followed consistently by significant disturbances. But since nightly sleep is so absolutely universal and refreshing, its failure to occur with satisfactory regularity in otherwise healthy persons always merits investigation, while it is age-old clinical experience that sleeplessness in patients already struggling with illness may be a most serious affair. Practically all who are unable to sleep fall into one of three categories: (*a*) those who experience great difficulty in going to sleep; (*b*) those who cannot remain asleep long enough to become completely rested; and (*c*) those who suffer from fitful sleep throughout the night. In a general way sleeplessness of the first sort is due either to excessive excitability in the cortex, as in some of the neuroses, or to the arrival there of excessively strong stimuli, as in instances of undue excitement or sorrow or the presence of pain, coughing, dyspnea, or the discomfort of a feverish state. Experience indicates that insomnia of the second type (inability to remain long asleep) is often associated with inflammatory or degenerative (such as arteriosclerotic) changes in the subcortical (brain stem) centers. The third type of insomnia, "the fidgets" of motor restlessness, is usually due to excessive fatigue or in some instances merely improper sleeping conditions as to bed, noise, temperature, light, etc.

THERAPY

Many physical, hygienic and psychotherapeutic measures need to be employed in luring and holding sleep, most of them too obvious to require listing here; but perhaps the mentioning of one or two little "extra dodges" may not be amiss. One is that there are many more people disturbed by noise than is commonly believed; individuals, that is, who sleep well enough once they sink into the state, but who are kept awake long after going to bed by what Horder (1934) aptly described as "appreciation of the fact that certain noises are need-

less and preventable." The trick here—and I shall not seek to make Lord Horder responsible for the remedy as well, of which indeed he may not approve—is to assure these people that there is ample ground for their peevishness, and that most impressive (one need not add rather hopelessly ineffectual) bodies of citizens are "dealing" with the matter in several countries, but that pending the arrival of blessed silence the only sensible thing to do is shut out the horrid jangle—then follows the advice to visit a sporting goods store for the purchase of a pair of the gadgets professional swimmers use to plug their ears while in the water. Thus one supplies sympathy, understanding and a remedy (only of course nowadays some people like to hear the bomb before it has whooshed right into the house). Many persons are sensitive to light, too. There are black shields, with padding for the hollows under the eyes, commercially available, but they quickly grow soiled and easily lose themselves. A black sock, fastened toe to top with a very small safety-pin, fits well over the head and is not excessively warm. Then, too, there is the matter of eating. Many individuals cannot sleep if they have recently eaten, therefore nearly all people think that late supper-eating is harmful. This is of course not based on fact, and some insomniacs will be actually relaxed by a bit of food taken just before going to bed. And finally, in just this last group especially, in rare instances blood sugar studies will reveal the insomnia as one of the manifestations of hyperinsulinism, dealt with elsewhere in the book.

When drugs must be used we would wish to have at our disposal agents that both quickly and reliably put the patient to sleep (or keep him asleep if early waking is his complaint) without upsetting the stomach or causing a preliminary period of excitement and without dangerously disturbing the cardiovascular or other physiologic functions; furthermore we do not wish to induce habitual dependence upon the drug or to cause cumulative poisoning through slow excretion. These are severe criteria and no hypnotic drug entirely satisfies them.

Barbiturates.—Urea, an end-product of protein metabolism and a constant constituent of the body, may be converted into a powerful hypnotic by a relatively simple type of treatment in the laboratory. By varying this treatment slightly, product after product has been produced, each having hypnotic properties but each differing markedly or slightly from all others in the speed, depth and duration of its action.

Seconal is a very rapidly acting barbiturate given in average adult dose of $1\frac{1}{2}$ to 3 grains (0.1–0.2 Gm.). *Amytal* does not act so rapidly but its action is somewhat more prolonged; it is given in average dosage of $1\frac{1}{2}$ to 5 grains (0.1–0.3 Gm.). *Pentobarbital* has a rapidity and duration of action somewhat like that of amytal; it is given in an average dose of $1\frac{1}{2}$ grains (0.1 Gm.). *Barbital* is so slow in action that it may require more than an hour to become effective; its average dosage is 5 to 10 grains (0.3–0.6 Gm.). *Phenobarbital* is the slowest acting of the lot but its effect is the most prolonged; its average dosage is $1\frac{1}{2}$ to 3 grains (0.1–0.2 Gm.). There are of course many more barbiturates available than those above listed but it seems to me that with this limited number the practitioner can accomplish anything desired. It is best to give these agents in the form of tablets or capsules because their soluble sodium salts break down too rapidly to enable them to be safely prescribed in bottle form. In many instances these barbiturates can be more effectively employed as sedatives than as hypnotics, *i.e.*, the hypnotic dose is divided into three or four portions and used at intervals throughout the day such as after

each meal and again at bedtime; phenobarbital is particularly well employed in this fashion in the type of insomnia accompanying a nervous jittery state. Some individuals experience a considerable "hangover" the next day following the use of a full hypnotic dose of barbital but the shorter acting members of this series offend less in this respect. Barbiturate ingestion occasionally causes skin eruptions and vague aches and pains about the body, and not infrequently habituation of an insidious and serious type is induced.

The Chloral Group.—Though possessing the advantage of being sufficiently soluble to prescribe in solution *chloral hydrate* is objectionable in taste and very irritating to the stomach; it is a cardiac depressant only in much larger than ordinary doses (Alstead, 1936). Twenty to 30 grains (1.2–2 Gm.) usually induce sleep within thirty minutes (occasionally brief excitement precedes sleep; very rarely the drug's only action is excitatory) but do not maintain it more than a few hours. The peripheral vessels being somewhat dilated by this dose (reflecting action on the vasomotor centers), the patient should be well covered if in a cool or breezy room. Residual symptoms on the following day are quite infrequent with chloral nor is it truly habit-forming, but insomniacs tend to hold on to any crutch even after they no longer need it. The following are typical prescriptions containing 15 grains (1 Gm.) in the teaspoonful, it being permissible to allow a second dose after an hour. The first has a fruity licorice taste, the second is acid sweet; neither disguises chloral very well but this cannot be helped. As a matter of fact, I think that too pleasant hypnotics such as the barbiturate tablets now in vogue are a habit-inducing curse.

℞	Chloral hydrate	ʒj	30.0
	Fluidextract glycyrrhiza	℥ij	60.0
	Syrup orange to make	℥iv	120.0
	Label: 1 teaspoonful well diluted one hour before retiring.		

℞	Chloral hydrate	ʒj	30.0
	Syrup citric acid	ʒj	30.0
	Water to make	℥iv	120.0
	Label: Same		

Until recently it has been held that the addition of alcohol to prescriptions containing chloral hydrate promotes the formation of chloral alcoholate (especially favored by the presence of bromides), a substance which was thought to be much more powerfully and rapidly acting than chloral hydrate itself. Adams (1940), however, failed to find any data in support of the alleged toxicity of chloral alcoholate, but it seems to me that nevertheless it is well to keep alcohol out of chloral-containing prescriptions.

Fantus (1936) recommended the following dosage of chloral hydrate for children, to be given in starch water as a retention enema: one to two months, $1\frac{1}{2}$ to $2\frac{1}{2}$ grains (0.1–0.15 Gm.); one to two years, 8 to 12 grains (0.5–0.8 Gm.); six years, 15 grains (1 Gm.); ten to fourteen years, 25 to 30 grains (1.5–2 Gm.).

Chloral is largely reduced to trichlorethyl alcohol and excreted in the urine within eighteen hours in combination with glycuronic acid (as urochloralic acid which gives a false positive sugar reaction with Fehling's but not with Benedict's solution).

Attempts to modify chloral under the mistaken idea that ordinary therapeutic doses are dangerously depressing to the circulatory apparatus have only served to weaken its hypnotic action; a possible exception is *butyl chloral hydrate*, which is given in capsules, 5 to 20 grains (0.3–1.2 Gm.), and is some-

times said to be of some value if the sleeplessness is caused by pain, as chloral hydrate certainly is not. Modification away from the gastric irritation has been more successful, and in *chlorbutanol* (*chloretone*) we have a product which is not only hypnotic but actually locally anesthetic, though very much milder than the cocaines and usually employed only as a dusting powder. Given internally, 5 to 20 grains (0.3–1.2 Gm.) in capsules or tablets, it slightly anesthetizes the gastric mucosa; it is therefore used as a sedative in vomiting and in attempting to prevent seasickness. I think the profession would do well to use this drug more often in insomnia, since it affords chloral hypnosis without gastric irritation.

Paraldehyde.—This drug is similar to and more rapid in its action than chloral but it more often produces excitement and occasionally an ordinary dose fails to be effective at all. It is a colorless liquid with odor and taste so disagreeable as very much to limit its use, and also it is more irritant to the gastric mucosa than chloral hydrate. Administration sometimes causes coughing, and the odor persists in the breath for a long time because the drug is partially excreted through the lungs (though principally in the urine). It is certainly less toxic than chloral in large doses, but since chloral is not at all dangerous in therapeutic doses paraldehyde probably has no advantages, particularly as it is prone to cause habituation despite its taste. Dose: ½ to 2 drachms (2–8 cc.) on crushed ice or in highly alcoholic vehicle, such as the tincture of sweet orange peel. The following is about the best that can be done, but it is none too good; perhaps diluting with sweetened iced tea instead of water, as Fantus suggested, may be worth while.

℞	Paraldehyde	℥ij	60.0
	Tincture sweet orange peel to make	℥iv	120.0
	Label: 1 to 4 teaspoonfuls well diluted upon retiring.		

Paraldehyde may also be given by rectum, diluting the dose well with water and giving as a retention enema; it is sometimes given intravenously in a dose of 1 cc. to obtain its full anticonvulsant effect, as in status epilepticus (see Epilepsy).

Alcohol.—Alcohol in the form of ½ to 1 ounce of whiskey, or a glass of wine or small quantity of beer, is a quick-acting and very reliable hypnotic in those accustomed to the taking of alcohol at other than bedtime, especially aged individuals; but it will likely excite teetotalers. The effect is not long-lasting because of the quick destruction of alcohol by oxidation, and of course the danger of inducing the habit of tippling must always be borne in mind.

Sulfonmethanes.—*Sulfonal* dosage is 10 to 15 grains (0.6–1 Gm.), best given in hot liquid, at least four hours before retiring; *trional*, in twice the dosage, acts in about half the time, though with both drugs action may be much delayed. Acute poisoning need not be feared with these doses but since excretion (unchanged in the urine) is very slow neither of the drugs should be administered more than two or three times without intermission of an equal period in order to prevent cumulative poisoning with confusion, ataxia, gastro-intestinal disturbances and kidney changes. Hematoporphyrin in the urine (pink or red color) is a warning sign. Because of general unreliability and the not infrequent fatal termination of poisoning cases, continuance of the sulfonmethanes in our armamentarium is doubtfully justified.

Bromides.—The bromides are not primarily hypnotics; however, they are often of value in one of two ways in aiding the patient to sleep: (*a*) in small

doses of 5 to 10 grains (0.3–0.6 Gm.) three times daily their sedative action overcomes the hyperexcitability responsible for sleeplessness in some cases; (*b*) given in a single dose on retiring (10–20 grains) in combination with a reduced dose of chloral they often prolong the sleep initiated by the latter drug. Gastric irritation, bromoderma and the other symptoms of bromism are objectionable features of bromide therapy, but one can usually detect this overaction before it has gone far (see Epilepsy).

Carbromal (Adalin) and Bromural.—These drugs are neither simple inorganic bromide salts nor barbiturates, though derived from urea and having some bromine attached. Either of them in a dose of 5 grains (0.3 Gm.) three or four times daily, or 10 to 20 grains (0.6–1.2 Gm.) an hour before retiring, is of value in the type of insomnia in which sedatives rather than stronger hypnotics are indicated. Bromoderma is apparently of very rare occurrence and habit-formation comparable to that with the barbiturates has not been reported. These drugs are insoluble and must be prescribed in capsules or tablets. When they maintain sleep for only a few hours it is permissible to give another 5 or 10 grains (0.3–0.6 Gm.) in the night.

Analgesic-Hypnotic Mixtures.—When the physician wishes to potentiate the action of a salicylate or a coal-tar analgesic by the addition to it of hypnotic drugs he should write his own prescription and not merely instruct the druggist to supply so and so many of a proprietary tablet or capsule containing these drugs in combination. Most of these preparations contain amidopyrine, which it seems to me we are no longer justified in using in this loose way—see Agranulocytosis. Furthermore, it is very bad practice to do no more for the patient than advise that he buy another little tin box or glass bottle full of the tablets he knows so well. The following is the sort of prescription which I have in mind; it contains 3 grains (0.2 Gm.) of acetanilid and $\frac{3}{4}$ grain (0.045 Gm.) of seconal per capsule:

℞	Acetanilid	gr. xxxvi	2.4
	Seconal sodium	gr. ix	0.54
	Make 12 capsules		
	Label: 1 capsule as directed.		

Acetphenetidin (phenacetin), or acetylsalicylic acid (aspirin), either in the amount of 1 drachm (4.0 Gm.), so that each capsule would contain 5 grains, might equally well have been used instead of the acetanilid. Indeed, aspirin itself, in a dose of 10 grains alone, is often astonishingly effective as a hypnotic in patients kept awake chiefly by petty annoyances and overfatigue—but it must be prescribed as acetylsalicylic acid in capsule form; aspirin purchased in tablets is not known as a hypnotic and the patient will scorn suggestion of its use for that purpose.

DELIRIUM TREMENS

This is a type of acute insanity that develops in a relatively large proportion of heavy drinkers of alcohol under any of the following circumstances: (*a*) after a particularly heavy or prolonged bout of drinking; (*b*) during the first few days of an acute infectious disease; (*c*) following trauma, particularly fractures and injuries to the respiratory tract; (*d*) following the sudden with-

drawal of liquor, these last cases being of extremely rare occurrence. After one or more days of prodromal uneasiness and insomnia, the patient begins to tremble and becomes actively delirious in which state he remains without sleep for an average period of five or six days and then slowly recovers or dies; 9 per cent of the 305 patients of Rosenbaum *et al.* (1941) had convulsions. The outstanding features of the delirium in typical cases are: first, the fact that the patient is aware of his own personality but is disoriented as to time and the outside world; second, that he is in a state of great fear; and third, that the hallucinations are of sight almost exclusively. The temperature remains normal in uncomplicated cases unless muscular activity is very great; the heart rate and force also correspond directly to the patient's activity except insofar as they are altered by previously existing cardiovascular disease. Delirium is usually superseded by heavy sleep of several days' duration. In severe cases the state of postdelirium stupor known as "wet brain" supervenes; delirium gives way to semicoma and tremor to immobility, and the patient lies upon his back making "rope-climbing" movements with his hands above his head. In fatal cases the body becomes rigid and coma deepens into death. The mortality in uncomplicated cases of delirium tremens is generally reported at about 15 per cent, but in some clinics which have been specializing in the treatment of this condition it is much lower: for example, Rosenbaum *et al.* (1940), at the Cincinnati General Hospital, reported 534 cases with a gross mortality of 2.5 per cent and a net mortality, after omission of complicated cases, of 1.7 per cent.

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Purgation.—It is routine practice in practically all emergency or general hospitals where these cases are frequently seen to attempt the administration of a brisk cathartic at once: either a large dose of the salines, or 3 grains (0.2 Gm.) of calomel, followed in four to six hours by a saline.

Sedation.—To produce sleep is of the utmost importance; but as a matter of fact the ordinary hypnotic drugs (see Insomnia) in any dosage likely to be safe are practically worthless. Paraldehyde is probably the exception; in 3- or 4-drachm (12 or 16 cc.) doses several times daily it is at least well borne if not always effective. Chapman (1944) said that at the Boston City Hospital they sometimes find it necessary to follow an initial 16 cc. dose with doses of 8 to 12 cc. every hour, control of the case usually being obtained, if other measures are adequate, in two or three hours (see Index for other methods of administering this drug). Sperber (1936) reported excellent results with the intravenous administration of sodium evipal, 2 to 3 cc. of a 10 per cent solution. The patients, who had to be manhandled in order to get the drug into them, went off to sleep at once, roused briefly after two to four hours, and than sank again into sleep for another eighteen to twenty-four hours; there was no sign of delirium upon final awakening.

Morphine is nowadays considered to be dangerous to use because of its alleged ability to increase intracranial pressure. Nor is there any longer any doubt that alcohol is contraindicated. Lambert wrote that apomorphine hydrochloride, 1/10 grain (0.006 Gm.), combined with strychnine sulfate, 1/30 grain (0.002 Gm.), often has excellent sedative qualities. Physical restraint as a method of treatment is no longer popular and is, indeed, looked upon by many observers as needlessly combating the sufferer.

Cerebral Dehydration.—A good many years ago spinal drainage and the use

of hypertonic solutions intravenously were separately reported upon. Cline and Coleman (1936) combined these methods and were very favorably impressed with their results during a two-year period in an active psychiatric institute. Their routine treatment consisted of the following: (*a*) spinal drainage of from 50 to 75 cc. of fluid; (*b*) intravenous administration of 50 to 100 cc. of 50 per cent dextrose solution; (*c*) magnesium sulfate by mouth, 1 to 2 ounces (30–60 cc.) of saturated solution; (*d*) limitation of fluid intake to 1000 cc. for twenty-four hours. Piker and Cohn (1937) also highly recommended spinal drainage and said that in approximately 1500 cases of acute alcoholism and delirium tremens they had never seen it do any harm, but they recommended that the fluid be allowed to escape slowly; and more recently, Rosenbaum (1941) of their group, finding that the spinal fluid pressure was normal in 75 per cent of 211 cases, indicated that while the measure is valuable it should be looked upon more as an aid to differential diagnosis than to therapy. The matter of fluid limitation has also come in for criticism recently. Piker (1938), of the Cincinnati group, studied 150 patients, half restricted to 1000 cc. and half given 3000 to 4000 cc. of fluid; his conclusion was that the advantage lay neither way. In fact this group of workers now seems to feel that the most important elements in therapy are hospitalization, spinal drainage, the use of paraldehyde and more attention to psychotherapy than has previously been the custom. However, other groups, such as Bowman *et al.* (1939), of Bellevue Hospital, favor the forcing of fluids unless there are contraindications.

Sodium Chloride, Carbohydrates, Vitamins.—It has been empirically observed that some patients are helped by the administration of both carbohydrates (with or without insulin) and sodium chloride in rather large amounts; some men therefore incorporate these measures in their plan of attack. Others have found thiamine hydrochloride (vitamin B_1) and nicotinic acid (niacin) of value, but Wortis (1940), reviewing the subject, found the evidence in favor of such vitamin therapy very meager. Nevertheless, Cannon *et al.* (1942) reported good results in a small group of patients from the use of large amounts of thiamine, concentrated dextrose solution and insulin, all given in one intravenous injection: 50 cc. of 50 per cent dextrose, 8 cc. of thiamine hydrochloride solution (about 25,000 units) and 25 units of insulin.

Supportive Therapy.—The whole gamut of these drugs is usually run, but it is not a matter of record how much is accomplished thereby. Piker and Cohn, in 1937, very much favored beginning digitalis therapy as soon as the diagnosis is made, and when digitalization is reached in thirty-six to forty-eight hours continuing with maintenance dosage until recovery is complete; their belief at least at that time was that to withhold digitalis in these patients until heart failure has set in is to court disaster.

A General Plan of Treatment.—From all of the above it will be seen that there is a bit of confusion and contradiction in the therapy of delirium tremens today. Therefore it may possibly be helpful to set down here a clear outline of the procedures as followed at Bellevue (Wortis, 1940):

(1) Withdraw alcohol abruptly.

(2) Give sedative medication judiciously, paraldehyde being preferred, and morphine condemned.

(3) Omit restraints unless absolutely necessary.

(4) Give carbohydrate in large quantities.

(5) Administer sodium chloride in an attempt both to combat dehydration and to restore the normal acid-base equilibrium of the body.

(6) Provide a high-calorie, high-vitamin diet.
(7) Force fluids.
(8) Do lumbar punctures for diagnostic purposes only.
(9) *Treat complicating or precipitating factors with specific therapy.*
(10) Give individual psychotherapy according to the needs of the patient.

SEASICKNESS AND AIRSICKNESS

There are some individuals who suffer from loss of appetite and low-grade nausea, but not actual vomiting, throughout the first few days of a sea voyage and then recover their normal feeling of well-being; others there are who experience only an excruciating headache without the least gastro-intestinal symptoms; but the symptoms in the most frequent type of the malady consist in discomfort in the epigastrium, anorexia, salivation, headache, dizziness, weakness, cold perspiration, greenish pallor, great dejection and bouts of vomiting with or without nausea. Most cases terminate spontaneously after a few days at sea, but there are individuals who suffer continuously throughout an entire voyage; according to Schwab (1943) sailors in War II sometimes developed definite psychoneurosis as a result of prolonged bouts of seasickness. Even professionals with many years of seafaring experience are occasionally made slightly ill when the ship begins to pitch or roll in an unusual fashion, particularly if they walk to a part of the vessel which they are not in the habit of visiting.

In airsickness the comparable bout of nausea and vomiting with all the accompaniments may be just as severe as in seasickness but under the conditions of ordinary civilian air travel the attack at most does not last more than a few hours.

These two types of motion sickness are placed here among the disturbances of the nervous system, but the truth is that despite the respectable antiquity of seasickness and the considerable interest that there is in airsickness nowadays, we are still without an entirely satisfactory explanation of the etiology of these profound upsets. Each of the following has at some time been urged as the sole cause of seasickness, and such of them as apply have also been proposed in explanation of airsickness also, but it is more probable that all of them operate to some extent in varying proportions in each case: (*a*) The labyrinthine theory, suggesting that the upset is caused by overstimulation of the equilibratory organs in the internal ear, with resultant overflow of stimuli from these to other centers, such as the vagus. (*b*) The theory that confusion results from the multiplicity of unusual stimuli coming along those sensory nerves that ordinarily have to do with the adjustment of our bodies in space. (*c*) The theory that there is excessive discharge along either parasympathetic or sympathetic pathways depending upon whether the individual is "vagotonic" or "sympatheticotonic." (*d*) The theory that eyestrain caused by the glare of the sea and sky, and the unusual fixation upon moving objects, reflexly causes the symptoms. (*e*) The theory that the wide excursions made by the freely movable organs of the abdominal cavity unduly irritate the vagus nerve. (*f*) The theory that autosuggestion is causative. (*g*) The theory that the malady is an acidosis.

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Postural Treatment.—Unless the psychic element is uppermost, the seasick patient probably profits most by lying supine with the head very little, if at all, raised. The nearer the center of the ship he stays the better. Sudden movements should be avoided, such as bending forward or getting up rapidly, or hurriedly ascending or descending the companionway. The only thing the unfortunate airsick individual can do is sit in the seat assigned to him, use a vomit bag, and hope that his fellow passengers are not too much annoyed by his loud goings-on.

Value of Fresh Air.—The seasick patient should recline on deck, if possible; however, many patients are embarrassed by their illness in the presence of others and can relax freely only in the privacy of their cabins, in which cases all facilities for maintaining the circulation of the air in the room must be utilized. In the air, the patient usually is able to control the ventilation over his own seat and probably does well to maintain a considerable stream of fresh air coming in upon him.

Prevention of Eyestrain.—The seasick individual should lie facing the deckhouse and not the sea and should avoid using the eyes as much as possible, reading only for brief periods and keeping the eyes closed at other times. Some persons immure themselves in a darkened cabin as soon as they board ship and leave it only when the port of destination has been reached. Perhaps a few thus avoid illness, but the fact should not be overlooked that blind persons also suffer from seasickness. I once watched a fellow air passenger who kept his eyes squeezed closed almost with the passion of a compulsion neurotic but who nevertheless gagged and vomited (not always too accurately!) throughout the four hours of the journey.

Plugging of the Ears.—The simple procedure of plugging the ears with cotton is said to relieve the symptoms of seasickness in some instances; what is put on the cotton is of course of no importance—indeed, I think the sole effect is psychic.

Abdominal Binder.—The use of a tight binder across the lower abdomen has many staunch supporters among experienced travelers at sea; most physicians believe that only those with visceroptosis are thus relieved. However, during my own brief experience as a ship surgeon one of my fellow officers repeatedly demonstrated to me that he became quite ill without his binder in a heavy sea. For all I know this man may have been visceroptotic but I do not believe that he was under any psychic thraldom to his belt, for he had followed the sea for many years and had only recently discovered that he could pass unscathed through storms in this way. I have seen no account of the use of an abdominal binder in the prevention of airsickness.

Diet at Sea.—On this head Oriel (1927) wrote: "One finds that if passengers can be persuaded to eat plenty of fruit and carbohydrates and to avoid fats that they are never violently sick. The common error is to avoid food, which, of course, leads to an early exhaustion of the glycogen reserve. Acidosis is the inevitable sequel. Once this train of events is in progress other factors, such as inability to take food and constant vomiting, tend to make the acidosis more severe." Seasick persons should eat, no matter if they lose one meal after another, for vomiting something is easier than the endless retching of an empty stomach. Swallowing small chunks of ice, or sipping cold ginger ale or champagne, is often a helpful measure in dispelling nausea.

Certainly the excessive smoking and drinking in which many individuals

indulge while at sea cannot but aggravate the bout of illness when heavy weather comes.

The following carminative mixture will hasten the passage of the stomach contents into the duodenum, and may prevent the onset of the complete syndrome in an individual who is only slightly nauseated:

℞	Tincture of capsicum	ʒss	2.0
	Spirits of peppermint	ʒij	8.0
	Tincture of ginger	℥ij	60.0
	Alcohol to make	℥iv	120.0

Label: 1 teaspoonful well diluted after meals; may be repeated if desired.

Dextrose.—The suggestion of Jones (1925), somewhat substantiated by the findings of Oriel (1927), that seasickness is an acidosis entirely curable by dextrose, was questioned by both Marrack (1931) and Maitland (1932), on the basis of much experience. It was not doubted by these latter authors, however, that dextrose given intravenously or rectally, or by mouth if it can be retained, is helpful in some instances.

Cathartics.—The normal individual should be warned that he is liable to become somewhat constipated during a sea voyage and will do well to employ a simple cathartic on any day that he has not gone to stool. I think the drastic catharsis induced by many voyagers before they board ship is unnecessary.

Atropine or Scopolamine.—Girard many years ago advocated the use of atropine sulfate, 1/120 grain (0.5 mg.), combined with strychnine sulfate, 1/60 grain (1.0 mg.) subcutaneously, at the beginning of a sea voyage, during rough weather, or on the advent of a storm; this dose to be repeated twice, at hourly intervals, or until incipient dryness of the throat and disturbance of vision indicate its discontinuance. Lundy (1938) quoted the surgeon of the Italian liner Rex as saying that 1/60 grain (1.0 mg.) of atropine alone and given intravenously will almost instantaneously bring relief. I believe that the attempts to prove the rationale of the atropine-strychnine combination, based upon the pharmacologic actions of its components, have not been fortunate; but it is certainly a clinical fact that the mixture does often relieve seasickness. Some men prefer scopolamine hydrobromide (hyoscine) to atropine. Holling *et al.* (1944), studying the matter under conditions of good control in the British Navy during War II, found scopolamine to be the most generally useful of all the drugs tried; initial dosage was 1/100 to 1/50 grain (0.6–1.2 mg.) and it was found feasible to give subsequent doses of 1/200 grain (0.3 mg.) at intervals of six hours. There were no disturbing side effects other than some drying of the mouth on the higher dosage. The only report of the use of scopolamine in the prevention of airsickness which has come to my attention is that of Haslam (1944), who wrote that he had been prescribing scopolamine with great satisfaction to his patients for a good many years. For short journeys he found that it sufficed to give 1/200 grain (0.3 mg.) four hours before starting and another dose of the same size as the flight began; for long air journeys he advised three doses at four-hour intervals.

Benzedrine (Amphetamine) Sulfate.—Hill (1937), of the prewar Aquitania, used this drug with good effect in 79 of 100 patients, though in only 39 was the improvement unequivocal. More recently, Albrecht (1943), while serving in the U. S. Coast Guard during War II, studied the action of benzedrine in 100 patients with adequate controls. Relief of varying degree was noted in 78

per cent of the patients, the drug being used in the dosage of 10 mg. *before* arising and 5 mg. (in a few very severe cases 10 mg.) twice more during the day. I have seen no report of the employment of the drug in airsickness.

Sedatives.—The whole gamut is of course run, but many men prefer chlorbutanol (chloretone) in doses of 5 to 10 grains (0.3–0.6 Gm.) in tablets or capsules, to all other drugs; it may be given three times daily if it is desired to induce sleep as well as control the vomiting. In my own brief experience I several times saw chloretone in 5-grain doses succeed when other sedatives had failed.

Morphine and Rectal Feeding in Excessive Vomiting.—Desnoes described his handling of these cases as follows: "Cases of excessive vomiting that tax our efforts at control are occasionally encountered. After the usual remedies are tried, including the mustard plaster applied to the epigastrium, from $\frac{1}{8}$ to $\frac{1}{4}$ grain (8–15 mg.) of morphine sulfate, administered hypodermically, combined with from 1/200 to 1/150 grain (0.3–0.4 mg.) of atropine sulfate, is the court of last resort. Provision must be made for the curious fact that the drug most potent in checking vomiting is followed by vomiting as a common aftereffect. After the patient awakes from the sleep induced by the drug, he should be directed not to raise his head from the bed for several hours. Iced brandy, champagne or strong coffee may be given through a drinking tube, but if nausea reasserts itself it is best to continue the administration of morphine, combined with atropine, in progressively descending dosage, using perhaps every four hours half the previous dose. If neither food nor water can be retained in the stomach for twelve hours or so, no time should be lost in resorting to rectal alimentation. The only substances of food value that can be absorbed from the lower intestine are amino-acids, simple sugars and alcohol. The old method of trying to maintain nutrition by the introduction of ordinary foodstuffs through the rectum has been shown to be inefficacious. Skimmed and pancreatinized milk may also be used, or the clysma suggested by Smithies: alcohol, 50 per cent, 1 ounce (30 cc.); glucose, 1 ounce (30 cc.); physiologic sodium chloride solution, sufficient to make 8 ounces (240 cc.). Karo corn syrup is a concentrated solution of practically pure glucose and is easily obtainable. This injection should be administered at body temperature by the drop method, with the patient on his back and the hips elevated; it should be repeated two or three times during the day. A bulk of 10 ounces (300 cc.) should not be exceeded. Needless to say, feeding by mouth should be resumed as soon as possible, commencing with such easily digestible articles as milk, bouillon tea, ice cream and arrowroot crackers."

Oxygen.—In a general paper on the uses of oxygen in 100 per cent concentration, Boothby *et al.* (1939) listed seasickness as a malady which is always benefited if not entirely controlled, but I have unfortunately not seen the account of the studies upon which this statement was based.

Psychotherapy.—Many individuals, especially first-trippers, agitate themselves into a very nervous state before they board ship and are almost certain to develop seasickness as soon as the ground swell is felt. In these cases it is perhaps advisable to use small doses of the sedatives for several days before the voyage is begun, advising the ship surgeon when possible what has been done in order that he may be guided in his medication during the first few days at sea; indeed, the carrying of a note to this officer, with a request for what is looked upon as "special care," often has a profoundly helpful effect

upon nervous individuals who dread the ordeal of a bout of seasickness alone on a large ship; upon the reaction of the plagued surgeon let us draw the charitable curtain!

With regard to airsickness, Witwer (1944) stated that in a study of this malady in 1000 trainees during War II the impression was gained that fear and nervousness accounted for almost all of the cases, which indeed seemed to be borne out by the observation that 70 per cent of the airsick pilots obtained some relief from placebo medication. However, it is well known that dogs, horses, cattle and sheep become seasick, though to be sure we cannot say that the same causative factors do not operate here also.

Helpful admonitions regarding conduct during an ocean voyage are the following: (*a*) divert yourself in the company of others as much as possible, but do not plunge too strenuously into unwonted exercise; (*b*) look shipward instead of seaward for the first few days, but do not "strain" yourself to do this else it will only serve as a reminder of the ever-lurking illness; (*c*) avoid the sight of sick individuals as much as possible; (*d*) go in jauntily to meals as soon as they are announced for procrastination often spells disaster at this juncture; (*e*) if on a small ship, keep to windward of the deckhouse in order to avoid the odor of cooking food.

GERIATRICS

(*The Care of the Aged*)

In recent times there has come to be a certain amount of fuss and bother about the necessary and impending reorientation of medical thought toward the diseases of the aged who are steadily increasing in numerical proportion in our population. In some quarters I know that before the war young men were being urged to specialize in geriatrics. For my own part, however, I am unable to become quite as disturbed by the new prospect as admittedly perhaps I should be. My "objections," if one wishes to call them that, are two, which will be developed below.

In the first place the analogy between pediatrics, the medical science at the one end, and geriatrics, the medical science at the other end of the span of life, is basically unsound. The reasons for this basic unsoundness have been expressed by Kniskern (1940) so much more ably than I could do it that I shall merely summarize his reasoning here. His position is that the child has no objection to being a child and knows that he will soon get over it, whereas the oldster has been dreading old age all his life and knows that it will not only continue but get worse. Furthermore, the aging individual firmly opposes admitting to himself or to anyone else that he is growing old, and he (perhaps even more positively she!) will certainly not willingly walk into the office of a physician known to treat only the diseases of the aged. So it seems to me that the young man who has chosen geriatrics as his specialty might do well to prepare for a practice confined almost exclusively to institutions and clinics, since he is not likely to have many fee-paying patients enter his own office.

In the second place a little thought regarding the "diseases of the aged" will reveal that there are very few entities which can be placed categorically in this class. Barker's (1939) 240 aged patients presented with the following complaints in the vast majority of instances: disturbances of the nervous system, disturbances of the digestive system, disturbances of the circulatory system and disturbances of the locomotor apparatus. Barker furthermore said that about 50 per cent of deaths among the aged are from circulatory disturbances, about 12.5 per cent from respiratory disturbances, about 12.5 per cent from cancer, about 8.5 per cent from diseases of the kidneys, especially chronic Bright's disease, about 6.5 per cent from diseases of the gastro-intestinal tract other than cancer, and the remaining 10 per cent from diseases of all other organ systems and from accidental injuries. Of course one needs to particularize a bit among these categories but there is certainly nothing very distinctive in this list. Therefore in what follows I shall merely have a little to say with regard to these entities and such other matters bearing upon geriatrics as seem to come within the province of this book, warning the reader in passing that not even the merest trickle from the fountain of youth will splash him as he turns the pages.

Circulatory Disturbances.—There is a chapter upon this subject elsewhere in the book, in the course of which such considerations as bear upon the age of the patient are given what I hope is due consideration. There is really nothing else to add at this place.

Respiratory Disturbances.—This subject too has a chapter of its own, and such of the entities as are of an infectious nature are discussed separately under their own titles in the chapter on infectious diseases. One might remark that tuberculosis causes death among the very aged only occasionally and that pneumonia, once the "old man's friend," is leaning away from him now that the sulfonamides and penicillin have come upon the scene. But pulmonary emphysema, which may lead to circulatory breakdown through overburdening of the right side of the heart, remains a serious problem.

Nephritis.—This subject, in both its acute and chronic phases, is discussed elsewhere in the book in a chapter of its own.

Gastro-intestinal Disturbances.—These ailments too have their own chapter. Perhaps it is pertinent to remark that it is the consensus that peptic ulcer is rare in the aged but that, when it is present, it is apt to be very severe; *i.e.*, if there is hemorrhage the bleeding is likely to continue for a long time because of the relative rigidity of the vessel walls, and perforation is of more frequent occurrence than among younger individuals. A note worth adding here is that the accelerated pulse indicative of continued bleeding may not occur in the aged. Meyer (1940) pointed out that if the activity of the ulcer is dependent on the digestive action of free hydrochloric acid and pepsin one would expect fewer perforations in the aged because of the diminution in the acid and enzyme; still, relatively more perforations occur. Dyspepsia in the aged, a less serious seeming matter, should nevertheless be investigated, for often dyspeptic symptoms are merely the signpost pointing toward the heart as the real cause of the trouble. Ivy (1939) said there is no reason to believe that constipation is more common in the aged than in younger individuals, remembering that constipation as a complaint may be present in a patient when true constipation is not. Nevertheless, rectal constipation often leading to fecal impaction is seen with greatest relative frequency in institutions for the aged, according to most observers. If soapsuds or milk and molasses enemas will not relieve the impaction manual removal must be resorted to. Lee (1944) expressed himself as a firm believer in colonic irrigation about once a week for elderly people. Diverticulosis is merely a nonsymptomatic radiologic diagnosis, but diverticulitis, which is an inflammatory reaction in a diverticulum, gives rise to symptoms and occurs usually in early old age. This is usually considered a surgical problem, but Meyer (1940) said that in his experience the majority of these lesions have become localized and resolved without extension or complications.

Finally, what to do with the aged individual whose symptoms point toward the need for a thorough gastro-intestinal study? Meyer (1941) well pointed out that there is a deplorable tendency to employ merely simple symptomatic treatment in such individuals, and he made a plea for full employment of all laboratory diagnostic aids. He is doubtless right and justified, but let us, please, be gentle and bring these oldsters gradually up to the barium and x-ray bout which would be a dreadful ordeal even for some of us prime and cocky youngsters.

Cancer.—Despite the contrary opinion of some kind friends of my book it still seems to me that this great subject, being still in essence surgical, is not one which I should include. However, a few notes regarding intractable pain seem in order.

New Methods of Employing Opiates.—The great drawback to the opiates is of course the fear of causing addiction, not that we are desirous of avoiding

this for its own sake since these patients are but waiting to die anyway, but addiction brings with it symptoms of its own and often so alters the patient's personality as to make the final ordeal additionally difficult for the family; furthermore, addiction implies diminishing analgesic returns per grain of morphine, dilaudid, or pantopon, and the cost of the necessarily large amounts of these drugs is often very great. Recently two measures have been described which merit mention here even though a thorough trial of them has not been made as yet. One is the combination by Slaughter *et al.* (1940) of morphine and prostigmine methylsulfate; they gave a reduced dose of morphine in 1 cc. of 1:2000 solution of the prostigmine salt and reported an apparent potentiation of the action of the morphine. The other is the employment of small morphine dosage by continuous intravenous drip, as described by Neuhof (1941). Morphine sulfate, in the quantity of $\frac{5}{8}$ grain (0.04 Gm.), is added to 1000 cc. of physiologic saline solution and 100 cc. of this solution (containing 1/16 grain, 0.004 Gm., of morphine) is given intravenously per hour continuously. This method was described for postoperative use, but I think that it might be made to fit into some desperate terminal cancer pictures since Neuhof ascribed to it remarkable analgesic action with almost complete absence of the other and objectionable morphine effects; of course for one already addicted the dosage would doubtless have to be raised considerably.

Cobra Venom.—This agent is very rarely of value but under some circumstances it may be worth trying on the off chance that it will give relief. Unlike the opiates it must be given over a considerable period before relief may be expected; thereafter the doses are given less often in order to maintain the effect. Greenhill's (1941) routine is typical: begin with $2\frac{1}{2}$ mouse units injected intramuscularly, raise the next day to 5 or 10 units, and continue this dosage daily for about a week; thereafter, if analgesia has been obtained the patient may be kept comfortable with two or three injections weekly, but if success has not been obtained by the initial seven days of injection it is useless to persevere. Cobra venom is said sometimes to cause nausea, vomiting and diarrhea and occasionally intense pain at the site of injection.

Intraspinal Alcohol Injection.—It now seems to be established that in the majority of instances intraspinal alcohol injections give relief which may last several months. Of course this is a radical procedure since the spinal cord may be injured, but the risk may certainly be taken in such cases as are under present consideration. In the chart on page 825, published by the kindness of Dr. Elias Lincoln Stern, of New York City, the sites for injections are shown. In what follows I present Greenhill's technic for injection in cases of pelvic malignancy to serve as model for this procedure:

"No preliminary medication is given because we wish to observe the immediate effects of the injection. Most patients with advanced carcinoma of the pelvic organs have much more pain on one side than on the other. The patient is placed on the side opposite to that where most of the pain is present. A pillow or pad is placed under the pelvis and side to elevate the sacral and lumbar portions of the spine, the back is arched as much as possible, the body is turned somewhat ventrally, and the head is lowered slightly. By placing the patient in this attitude we raise the sacrolumbar region of the spine to the highest level and at the same time make the posterior or sensory nerve roots lie horizontally. The anterior or motor nerve roots come to lie in a plane which is usually out of reach of the alcohol. Even if the motor nerves are not removed from the field of the alcohol, as occurs in the cauda equina, they are not often

affected because sensory nerves are more susceptible than motor fibers to the effects of alcohol.

"Someone should hold the patient in the proper position. A weak solution of iodine or other antiseptic is applied over the lumbar and upper sacral regions. Injection is made in the second, third or (usually) fourth lumbar interspace. An ordinary lumbar puncture needle with a stylet is used. The needle is inserted into the desired interspace just as for an ordinary lumbar puncture, and novocain is injected into the skin before inserting the needle. After the needle is in the subarachnoid space, as evidenced by the flow of spinal fluid, 0.75 cc. of absolute or 95 per cent alcohol is injected into the cerebrospinal fluid. For this purpose it is best to use a tuberculin syringe in order to make sure that not more than 0.75 cc. of the solution is injected. Furthermore, the alcohol must be injected very slowly, drop by drop, allowing about two minutes for the injection of the 0.75 cc. The alcohol rises immediately to surround the posterior roots because the specific gravity of alcohol is about 0.806, whereas that of the spinal fluid is 1.007 to 1.011. No attempt should be made to draw spinal fluid into the syringe to mix it with the alcohol; in fact, this is exactly what is not wanted. After the injection is made the needle is withdrawn and the puncture hole is covered with sterile gauze and adhesive.

"Before the injection is completed, the patient will complain that the upper leg feels numb or hot, and that the leg cannot be moved. The *numbness* is almost routinely experienced after the injection but disappears spontaneously after a few hours or few days in most instances. In spite of what the patient says concerning inability to move the leg, when he is requested to move it he will meet no difficulty. At the time the patient informs us of the numbness he also often tells us, either voluntarily or in answer to our query, that the pain has disappeared. The longer the patient is permitted to lie on the side, the better the results. Hence, the patient should be kept on the side for two hours after the injection, after which period he is permitted to get up and walk around. Sometimes a patient finds difficulty in getting up from a chair because his "leg is asleep." In other instances the leg feels heavy and the patient experiences some trouble in walking up steps because the knee flexes readily. These sensations usually wear off in a few hours, although in some patients they last a number of weeks.

"Nearly all of the patients who are ambulatory may be permitted to go home within three hours after the injection. No ill effects will be observed from this procedure. It is perhaps best, however, to keep a patient in a hospital for twenty-four hours after an injection. I should like to emphasize that the intraspinal injection of alcohol may easily be carried out in a patient's home. This is important to remember because many individuals with cancer are bedridden at home and there is no need to subject them to the inconveniences and expense of transportation to a physician's office or a hospital.

"If the patient has pain on *both* sides, an injection is made a week later with the patient lying on the opposite side. The same amount of alcohol is injected."

Other Measures.—Nowadays several types of nerve section are available, but of course the selection of cases suitable for these operations requires the very specialized skill of a trained neurological surgeon. Latterly refrigeration and "hibernation" (crymotherapy) have been employed experimentally but these methods have certainly not reached the stage of general practical application nor would it seem that they are likely to do so.

Diabetes Mellitus.—Here is a disease which affects the aging more than the truly aged; it has a chapter of its own elsewhere in the book.

OUTLINE FOR REGIONAL ALCOHOLIC PAIN BLOCKING*

Organ involved.		Type of block.	Site of injection.
Head		Trigeminal block	I, II, III divisions: (*a*) Terminal nerves (*b*) Subganglionic block (*c*) Gasserian ganglion block
		Stellate ganglion sympathetic block	(*a*) Paravertebral, between first and second ribs (*b*) Subarachnoid T 1–2. Especially important in connection with trigeminal pain or neuralgia
Neck		Cervical plexus block	Paravertebral
Upper extremity		Subarachnoid block	T 2–3 Exceptional, T 1–2
Chest	Larynx Trachea Bronchi Lungs Heart†	Subarachnoid block	T 3–4
	Aorta† Esophagus†		Upper part T 3–4 Lower part T 8–9
	Pleura		Entire T 6–7 or T 7–8 Upper part T 3–4 Lower part T 8–9
Abdomen	Aorta† Spleen	Subarachnoid block	T 5–6
	Stomach† Liver† Pancreas† Small intestine†		T 6–7 or T 7–8
	Colon†		T 11–12 or T 12–L 1 Ascending and transverse colon T 4–5
	Kidney-suprarenal gland		T 11–12
Pelvis	Ovaries Testicles Uterus† Tubes Ureters Seminal vesicles Prostate† Urethra† Bladder†	Subarachnoid block	T 12–L 1 and L 4–5
	Rectum—anus†		L 4–5
Lower extremity		Subarachnoid block	T 11–12 (Sympathetic) and L 1–2 (somatic)

* In blocking the long viscera, aorta, small and large intestines, or in special cases, it may be necessary to repeat the block one or several segments higher or lower than the levels given above.

This outline applies only to the adult body.

† Lesions affecting these organs usually involve the sympathetic nerves of both sides. Bilateral (right and left) injections should be given in these cases.

Fractures.—The breaking of a bone, which used to be viewed as an unmitigated calamity for an oldster, is nowadays not nearly so serious a matter, thanks to the orthopedic surgeons who are insisting upon active movements immediately after recovery from the anesthetic.

Prostatism.—Here is certainly a distinctive disease of the aged, the hypertrophied prostate, a urological matter which of course has no place in this book. Spinal anesthesia, the transurethral resection technic, and the sulfonamides are a triad to which the world's old men should erect a monument. Clark (1939) performed prostatectomy under general anesthesia in a remarkable Negro man aged 110 years, who came into the clinic one year later to report himself very well!

Other Surgical Matters.—In this field, which is likewise outside the province of this book, great advances have also been made so that nowadays even elective surgery is performed in individuals of quite advanced years. Some factors which have contributed to this happy state of affairs in recent times are: (*a*) recognition of the necessity for painstaking preoperative measures to prevent postoperative complications by eliminating them "at the source" where possible; (*b*) the gradual passage of anesthesia into trained hands coupled with the introduction of less toxic general anesthetics and the increasing employment of spinal anesthesia; (*c*) postoperative care designed to oppose atelectasis by ensuring complete ventilation of the lungs, *i.e.*, the inhalation of carbon dioxide at intervals; (*d*) the attempt to prevent pulmonary embolism through centripetal massage of the legs and active and passive movements of the limbs in order to promote venous return as much as possible; (*e*) recognition of the necessity to get these old people up out of bed and moving around on their own power as soon as possible in order not only to prevent thrombosis but also the type of cardiac failure which may result from loss of cardiac reserve while lying in bed (and old people become terribly depressed in bed too, feeling that now at last their time has come); (*f*) the recognition that fluids should be "pushed" only very slowly if at all in these patients and that any measures—venoclysis, hypodermoclysis or proctoclysis—which keep the patient long on his back are likely to be extremely dangerous; (*g*) the use of the sulfonamides.

Eyes and Ears.—Cataract and glaucoma, and degenerative and vascular changes of the eyes, are predominantly diseases of the aging and the aged, as is also impairment of hearing. But it cannot be expected that a discussion of such things will be found in a book of this nature.

Diet and Vitamins.—It has been known for some time that hydrochloric acid and pepsin secretion decrease with advancing years, and now recently the information has been added that salivary and pancreatic (except amylase) secretions also diminish. But Meyer and Necheles (1940), who carefully studied these matters, found that the secretory mechanisms are capable of response under adequate stimulation and that the quantitative alterations apparently do not affect intestinal digestion. They concluded that restrictions imposed on old people because of fear of inadequate digestion of carbohydrate, protein, or fat do not appear warranted. In other words, old age in itself is no reason for dietary alterations. Experience has shown in fact that with few exceptions old people select both the quantity and quality of food which satisfies their needs and taste, and I do not think there is much fact to support Tuohy's (1943) warning that they should eat very sparingly of fats. Loss of appetite, however, is a matter which often requires serious attention. It may

be due to loss of teeth or poorly fitting false teeth which necessitate a change to a soft unattractive diet and ultimately lead to a loss of interest in food. Then, too, there are changes in the taste buds and diminution in the senses of sight and smell. To stimulate such lagging appetites bitters have long been used before meals, such as a teaspoonful in water of the compound tincture of either cinchona or cardamom; or a little dry wine to be taken with the principal meal of the day. Lee (1944) said he had come around again to a belief in the efficacy of "digestive assistants" in the elderly, *i.e.*, hydrochloric acid, pepsin, pancreatic extracts and the bile salts; I imagine not many observers would agree with that position. Latterly, thiamine hydrochloride (vitamin B_1) has begun to be used with apparently excellent results—dosage is usually a 3-mg. tablet after meals once, twice, or thrice daily as indicated by results. There are undoubtedly cases in which the prohibition of tobacco smoking would be helpful in stimulating the appetite, but the advisability of attempting such a radical deprivation must be carefully weighed in each individual case. In this group of elderly individuals with jaded appetites, and especially in those with dietary restrictions self or otherwise imposed, true vitamin deficiencies can now and then be found.

Disturbances of Locomotion.—In speaking of the infirmity of old age we probably most frequently have in mind the weakness in the legs and difficulty in locomotion which so often accompany the state. It seems that stiffening of the joints results to a considerable extent from failure in lubrication as well as from aging of the nerves and muscles. Some of the cases are of course due to osteoarthritis, fibrositis, or gouty arthritis—subjects which have a section of their own in the book. And then there is the group of cases which lies entirely within the realm of the neurologists, the relatively rare cases of senile paraplegia and senile cerebellar and amyostatic syndromes; I believe there is nothing to do for these latter save make the diagnosis.

Neuropsychiatric Disturbances.—Many old people develop tremor, particularly of the head, which is very annoying and embarrassing to them, but about the best one can do in these cases is to give assurance that the shaking is not a forerunner of paralysis agitans and is not as noticeable anyway as the patient thinks it is. True paralysis agitans with its characteristic flexed position of the extremities, bent-over posture, shuffling gait and general rigidity combined with tremor is a truly unfortunate affliction for which practically nothing can be done. The drugs used to combat postencephalitic parkinsonism are of course tried (see Encephalitis), but their effectiveness is usually slight here. If every effort is made to remain active both physically and mentally it is sometimes surprising to observe the small extent to which this degenerative process limits the individual's participation in daily affairs. The tendency to become dependent upon another, usually the husband or the wife, for the performance of most acts must be rigorously opposed from the beginning.

The aged often do not sleep well at night, being not so much disturbed in their sleep as simply sleepless. Sometimes daytime napping makes up some of the loss, indeed this is almost universally the case. However, insomnia in the aged, though often the subject of bitter complaint, is rarely a matter of serious concern for it seems that the aged body actually requires to spend a smaller proportion of the twenty-four hours in slumber than does that of the person in early or middle life. The happiest solution is for the aged individual to find something to do—read, play solitaire, etc.—while the younger members of the family are getting their needed sleep. Certainly one should be very chary

of employing hypnotics in these oldsters for they sometimes react in a very excited manner to these drugs; the bromides and barbiturates seem to be the worst offenders in this respect. Alcohol is the safest nightcap if one is to be employed at all.

The mental deteriorations pacing the advancing years are too well known to require more than mere listing: disinclination to accept anything new in either ideas, foods, or habits; failing memory, especially for recent events; excessive worry about the financial future; suspicious tendencies; and an increasing sensitiveness, so that we say "grandma is so easily 'hurt' nowadays." The summed expression of these things depends entirely upon the individual and the family environment—if luck is good the oldster may become the dearest and most charmingly influential member of the household; but luck is not always good.

The true senile psychoses must be left to the psychiatrists, it seems to me. They have done a deal of describing and classifying of them, and certainly should be called in before the awful step is taken of committing any patient. Some alleged senile psychoses have turned out to be only toxic states which have cleared up under proper eliminative and supportive therapy. I believe it is now the consensus that Robinson (1941) was correct in stating that shock therapy may be safely employed in the aging individual and that in some instances the senile process seems to be arrested.

DISEASES OF THE SKIN

IMPETIGO CONTAGIOSA

Impetigo is an acute contagious disease of the skin with a predilection for the face. It is sometimes spread among adult males by barber-shop infection, and an occasional case is seen in an adult female, but the great majority of patients are children within the school years. There are a number of varieties of this malady, but the most common one is characterized by a sudden crop of localized erythematous areas, upon which rapidly appear thin-walled vesicles and bullae; these lesions soon become pustular and then dry up quite rapidly, leaving thin, honey-colored, loosely attached crusts that drop off without scar formation, though the hyperemia fades out of the affected areas rather slowly. There is usually no itching. Both staphylococci and streptococci have been obtained from the lesions.

THERAPY

Sulfonamides.—Winer and Strakosch (1942) treated 60 patients by local application of 5 per cent sulfathiazole ointment and found cure effected in a considerably shorter time than with any other type of treatment which they had used before. There have been many similar reports since that time; for example, Peterkin and Jones (1943) effected cure in 120 cases in the average time of 6.8 days against the average time of 14.6 days in patients otherwise treated. In the Military Manual of Dermatology (National Research Council, 1942) it is stated that 5 per cent sulfadiazine ointment, rubbed in three or four times daily, will in most cases effect complete cure in four to six days, but Peterkin and Jones found both sulfadiazine and sulfamethazine less satisfactory than sulfathiazole. Harris (1943) reported the treatment of 15 cases of impetigo in children as follows: a few drops of a 20 per cent solution of "microcrystalline" sulfathiazole was poured onto a small gauze dressing and the side of the dressing on which the crystals precipitated was then placed in contact with the lesion which had previously been washed with ordinary soap and water and had all of its crusts removed; it was said that upon removal of the dressing twenty-four hours later the lesions were always found to be healed; Bigger and Hodgson (1944) also used the microcrystalline preparation satisfactorily in adults. This is all very fine, but I certainly think Sharlit's (1943) warning against the local employment of the sulfonamides in such benign affairs as impetigo should be well heeded since sensitization thus induced with these drugs may deprive the patient of their employment at a later time against some serious systemic infection.

Penicillin.—Johnson (1944) reported 12 patients who became clinically clear of infection in from three to seven days after the local application of penicillin-containing pads was begun; 4 of the patients had been previously treated with sulfonamide compounds without improvement. It will remain to be seen whether time will justify the use of penicillin in this way.

Ammoniated Mercury.—Perhaps the classical treatment of this condition is to cleanse the parts thoroughly with soap and water, breaking all bullae with gauze or a sterile toothpick, and then to apply an ointment of 1 to 2 per cent ammoniated mercury, sometimes increasing to as much as 10 per cent.

This used to suffice to cure most cases in one to three weeks, but of course to keep a grease applied to the face during working hours is objectionable to adults. In children this objection does not apply for they should be kept out of school in any case. I say "used to" advisedly, for it seems to be the opinion of numerous dermatologists that ammoniated mercury is not today as effective in impetigo as it was some years ago. The rare but often very severe idiosyncratic reactions to mercury preparations employed in childhood were reviewed by Gibel and Kramer (1943).

Colloidal Calomel.—At the Cook County Hospital, Cornbleet *et al.* (1939) used an ointment containing "colloidal" calomel, which they said cleared up the cases in one-third to one-half the time required by ammoniated mercury.

Gentian Violet.—This agent, usually painted on the lesions in 1 to 2 per cent aqueous solution, has become very popular in recent years, but I have seen no report of its extensive employment in direct comparison with the other agents—would it not, in fact, be worth the while of one of the large dermatologic clinics to make a controlled and comparative study of all the preparations which are currently being applied in the treatment of this condition?

Quinoline Compounds.—In a small number of cases, Seldowitz (1940) used a rubber base containing 8-hydroxyquinoline with very satisfactory results, the crusts disappearing in an average time of three days and the skin regaining its normal appearance in eight days. The lesions are covered with a thin layer of gauze and the rubber is applied over the gauze, the dressings being held in place with adhesive plaster and changed every two to four days. Carpenter (1938) earlier reported the use of an ointment containing 0.25 per cent chlorhydroxyquinoline and 5 per cent benzyl peroxide in equal parts of hydrous wool fat and petrolatum; results seemed to be at least equivalent to those obtained in his control ammoniated mercury cases. The Military Manual of Dermatology (National Research Council, 1942) recommended the application two or three times daily of the following ointment:

	Gm. or cc.
Chlorhydroxyquinolines (mixture)	0.5
Benzoyl peroxide (explosive)	10.0
Oil of white thyme	0.65
Eucalyptol	1.3
Petrolatum,	
Anhydrous lanolin, of each, to make	100.0

Silver Nitrate.—Morrow advocated the use of silver nitrate applied with a swab in 20 per cent solution after cleansing the lesions and opening the bullae. He and others found this treatment very efficacious, but open to two objections: first, that there is some pain on application of the solution, and, second, that a black unsightly crust appears quickly and remains for three or four days. Sutton used only a 10 per cent solution; the Military Manual (1942) recommended 2 to 5 per cent. The organic silver preparations (argyrol, etc.) have been found ineffective. After the application of the silver nitrate solution, Highman applied an ointment of ammoniated mercury or 10 per cent balsam of Peru.

Dusting Powder.—Morrow wrote: "It is advisable to apply a dusting powder, preferably one containing ammoniated mercury in the strength of from 6 to 10 per cent, and a boric acid powder up to from 15 to 20 per cent. When impetigo is on the uncovered part, even without the silver, the powder form of treatment should be selected in preference to a grease. Customarily I have

applied such a powder after swabbing with silver solution, and order its use by the patient several times daily."

℞	Ammoniated mercury	ʒiss	6.0
	Zinc oxide	ʒv	20.0
	Talcum to make	ʒij	60.0
	Make a dusting powder.		
	Label: Apply as directed.		

℞	Boric acid	ʒiij	12.0
	Zinc oxide	ʒv	20.0
	Talcum to make	ʒij	60.0
	Make a dusting powder.		
	Label: Apply as directed.		

Salicylic Acid.—Lain stated that after the secretions and scabs were removed by cleansing methods, he applied a 50 per cent alcoholic solution of salicylic acid in cases in which it was thought the patient could stand the treatment. This does not stain unless repeated and, in his hands, was of especial value in preventing spreading.

Iodine.—One per cent iodine in alcohol is sometimes used to paint the lesions; the stain does not persist so long as that of silver nitrate.

Metaphen in Collodion.—Hollander and Hecht (1934) washed with soap and water and dried the skin around the infected area and then painted the lesion with several layers of metaphen 1:500 in collodion. In twenty-four hours they took off the removable layers and reapplied the mixture, repeating the procedure on the third day; on the fourth day all layers were removed, including the underlying encrustation—if the surface was still moist reapplication was made, if dry 2 per cent ammoniated mercury ointment was used.

Copper and Zinc Sulfate.—Brownson wrote: "In my opinion there is little need for treating the ordinary cases of impetigo so actively. I have used a modified form of *l'eau d'Alibour*, the favorite treatment of Saboraud. A modification of his remedy, which does very well, is made up of 1½ grains (0.1 Gm.) of copper sulfate and 3 grains (0.2 Gm.) zinc sulfate to the ounce (30 cc.) of camphor water. I often start by removing the crusts by a boric acid-starch poultice, and when removed, sop on the solution named several times a day, and its results are usually prompt. It is cleanly, and I can hardly see how it could be improved on. I think the results are fully as good as when stronger applications are used." In conjunction with this treatment he sometimes used 1 per cent ammoniated mercury ointment at night, washed it off in the morning with soap and water, then applied the lotion during the day. Morris (1943) also recommended d'Alibour's solution.

TINEA VERSICOLOR

This malady is characterized by the presence, usually only on the chest and shoulders, of a yellow or brown macular eruption that sheds very fine scales. There are usually one or more large plaques with numerous small lesions round about them. Itching is slight or entirely absent. The disease, which is caused by *Microsporon furfur*, is rather common among men, but is entirely harmless. A few cases involving the scalp have been reported in Europe and in both North and South America, a distribution which is said to be fairly common in the Far East.

THERAPY

Tinea versicolor yields readily to frequent applications of a saturated solution of sodium thiosulfate (sodium hyposulfite), but only if the affected areas are first vigorously scrubbed with soap and water and then dried before making the application. If the solution is also saturated with thymol it keeps indefinitely without the appearance of mold. Crocker, cited by Sutton, found the use of 5 per cent solution of thiosulfate, followed by 3 per cent solution of tartaric acid, to be even more efficacious.

ERYTHEMA MULTIFORME

This disease is characterized by the rather sudden appearance of red to violaceous inflammatory lesions that, as the name implies, are multiform; they may be macular, papular, vesicular, or bullous. The sites of predilection are the face, neck, arms, hands, legs and feet. Except for the extremely rare instances in which there are serious systemic manifestations, subjective symptoms are few or none, but the attack usually lasts from two to three weeks and the individual may be afflicted time and time again. The etiology is unknown, though many observers are inclining to the belief that this malady will eventually be placed among the allergic diseases; *i.e.*, that it is an allergic reaction to a drug or to some article in the diet. Many men feel that the attacks are often due to a toxemia of intestinal origin. Anderson (1945) stated his feeling that there might be an etiologic relationship between erythema multiforme and herpes simplex, but the dermatologists discussing his paper did not seem inclined to support the hypothesis on the basis of either clinical or experimental observation.

THERAPY

Inquiry into what drugs are being taken should be made; arsenic, mercury, the iodides and phenolphthalein seem to be the chief offenders. Dieting and the taking of copious amounts of water are sometimes of value; perhaps the newer approach to food allergy might well be tried in recurring cases. At the New York Skin and Cancer Hospital we used always to give an initial dose of castor oil and then keep the patient on the Bulkley diet of rice (without sugar or cream), bread, butter and water as long as he would cooperate—treatment that, plus the forcing of fluids, was thought to lessen considerably the duration of an attack. For local application, calamine lotion may be used (see Index). There is no evidence that any of the internal remedies that have been recommended are of any use.

EPIDERMOPHYTOSIS OR DERMATOPHYTOSIS

(*Ringworm of the Hands, Feet, Groin, Axillae, Breasts and the Hairless Skin Generally*)

This is a skin disease that in one form or another seems to afflict most people all over the world, being especially prevalent in moist tropical regions; indeed, during War II in some instances it posed a rather serious military problem. *Trichophyton gypseum* and *T. purpureum* are most frequently recovered from the lesions and *Epidermophyton inguinale* is found perhaps less often. Dermat-

ologists seem to switch about between the terms epidermophytosis and dermatophytosis, but it seems to me that we should leave the vulgar "athlete's foot" to the vendors of nostrums and the writers in popular magazines. The principal forms of the disease are the following: (1) vesicular or scaling, seen principally on the fingers, toes, palms and soles; (2) macular, which is of two sorts, one (eczema marginatum, jockey-strap itch, Dhobie itch), the well-known red definitely marginated lesion occurring principally in the groin region, the axillae and beneath the breasts; and the other (tinea circinata, ringworm of the body), the slightly elevated ringlike patches that occur principally on the face, neck and hands; and (3) macerated, the familiar lesion between the fingers or toes and beneath the breasts, presenting as an area of clean, white, sodden tissue of a varying degree of thickness. There are several other forms less frequently encountered.

The disease is certainly contagious but the problem of protecting against it, seeing its ubiquity and protean character, is a very difficult one indeed.

THERAPY

Treatment of epidermophytosis has never been entirely satisfactory, some cases resisting any and all sorts of measures, while others clear up very quickly under the simplest treatment (I distinctly remember cases, seen while working in Williams' clinic at the New York Skin and Cancer Hospital, which rapidly cleared up under boric acid ointment being used at the time as a placebo). Attempts to desensitize the gradually increasing amounts of the offending agent in the form of the preparation known as "trichophytin" are perhaps logical but they do not seem productive of significant results, Traub and Tolmach (1935) having reported "little if any" effect on the course of the malady in 135 patients. The Military Manual (below referred to) also stated that these preparations are not to be recommended. Traub and Tolmach (1938) also reported that little was to be expected at present from convalescent serum.

One could easily fill ten pages of this book with the formulae of preparations that have allegedly at one time or another been curative in this malady, but since none of them are effective in all instances I shall content myself with condensing here the recommendations of Pillsbury *et al.* (1942) in the Manual of Dermatology published for the armed forces under the auspices of the National Research Council, merely appending a description of the use of ethyl chloride, which seems very promising nowadays.

Active Acute Stage.—The following general-Army-issue foot powder should be employed:

	Gm. or cc.
Salicylic acid	2.0
Boric acid	6.0
Zinc stearate	3.0
Exsiccated alum	1.0
Starch	10.0
Powdered talc	78.0

Alternate formula

	Gm. or cc.
Zinc peroxide	10.0
Tannic acid	5.0
Boric acid	20.0
Bentonite	10.0
Talc	55.0

Whenever possible hot potassium permanganate soaks should be used for twenty minutes three times daily, employing the solution made by dissolving one 5 grain (0.3 Gm.) tablet of potassium permanganate in 3 quarts of water. Much stronger solutions (up to 6 per cent) may be painted on areas of ringworm on the body. After the potassium permanganate soaks, the following lotion should be applied:

Sulfur	ʒi	4.0
Resorcin	ʒss	2.0
Zinc oxide	ʒvi	25.0
Talc	ʒvi	25.0
Bentonite	ʒi gr. xv	5.0
Water (or water and alcohol equal parts)	℥ ii	60.0

Twice daily the fissures should be painted with 5 per cent silver nitrate solution. If there are vesicles they will have to be aseptically opened before beginning the treatment.

Subacute Stage.—When the acute stage subsides in the typical lesions of the foot, the vesicular patches are replaced by scaling red patches and thickening, maceration and fissues of varying depths may develop. In this stage the treatment is the same as the above except that the following are added, either one of these ointments to be applied only at bedtime; one should be particularly on watch for evidences of irritation when using the Whitfield ointment.

Pragmatar Ointment

		Gm. or cc.
Sulfur	gr. xlv	3.0
Salicylic acid	gr. xlv	3.0
Cetyl tar distillate	ʒi	4.0
Duponol	gr. xv	1.0
Petrolatum	ʒixss	38.0
Stearyl alcohol	ʒivss	18.0
Cetyl alcohol	ʒi gr. xlv	7.0
Mineral oil	ʒvi gr. xv	25.0

Whitfield's Ointment (One-Half Strength)

Salicylic acid	3 per cent
Benzoic acid	6 per cent

White ointment (U.S.P. XII) to make.

In some cases in the subacute stage one may cautiously apply one of the following, the first being known as Castellani's Paint:

Saturated alcoholic sol. basic fuchsin	10.0
Aqueous solution phenol (5 per cent)	100.0
Filter and add:	
Boric acid	1.0
After two hours, add	
Acetone	5.0
Two hours later, add	
Resorcin	10.0

This preparation does not keep over one month.

Salicylic acid	3.0
Thymol	1.0
Alcohol (70 per cent) to make	100.0

Chronic Stage.—The lesions on the body do not tend to become chronic. Those between the toes and on the feet do very frequently resist treatment

and assume one of the following forms: if in between the toes the lesions are likely to be sodden, odorous patches with fissuring; or there may be thickened hyperkeratotic plaques with scaling, fissuring, or even vesicles on the soles; or red, thickened and indurated dry plaques on the sole, around the heel and along the sides of the feet. For such chronic cases the list of recommended agents is increased by the following:

Deek's Ointment

Salicylic acid	2.0
Oil of eucalyptus	12.0
Bismuth subnitrate	12.0
Wool Fat,	
Ammoniated mercury ointment, of each, to make	100.0

Apply at bedtime only.

Dioxyanthranol Ointment

Anthralin (or cignolin)	0.1–1.0 per cent
Petrolatum, to make.	

Apply cautiously once or twice daily to chronic hyperkeratotic and scaling placques.

Chrysarobin Ointment

Chrysarobin	0.1–0.5 or even 5.0 per cent
Petrolatum, to make.	

The chrysarobin must be fresh and the ointment freshly prepared.

The Manual also recommended the very cautious trial of the camphor-phenol mixture which was so much exploited after its introduction by Francis a few years ago. However, since Glenn and Hailey (1943) showed that this mixture is not beneficial, and since its use has resulted in the development of serious ulcerative lesions when applied to the wet skin, I feel justified in omitting the formula here.

These chronic lesions should be kept clean and if necessary hyperkeratotic material is to be removed by the use of sandpaper, curets, scissors, or the like. Superficial x-ray therapy has been said to be helpful in selected cases.

Ethyl Chloride.—In 1929 Taylor reported excellent results in a small series of cases in which he froze the lesions with the ethyl chloride spray. One heard very little more of this treatment until recently, when Bograd (1943) stated that in the South Pacific during War II the ethyl chloride treatment of lesions of the tinea group gave uniformly excellent results. Bograd said that there were no contraindications to its use, even though the lesions be covered by pustular eruptions due to secondary infection, and that the length of treatment depended solely on the age of the infection and not on the area covered. He stipulated that all of the lesions must be treated at one sitting and that no other drugs be used in conjunction with ethyl chloride, fungicides in ointment bases being particularly effective in retarding healing. The ethyl chloride is applied daily, being sprayed on until the temperature of the skin has been lowered sufficiently to bring out the white surface. If the lesion is a vesicle it is not opened but the spray is applied to the whole area; if it is a macule or larger the spray is applied around the edge and two to four applications are made, depending on the size. In instances of tinea circinata which has spread peripherally with actively inflamed raised margins hiding the vesicles, the whole raised margin is sprayed once daily for two successive days, and with the disappearance of the inflammation the discrete vesicles which become

prominent are treated as though they were primary lesions. With the more resistant lesions of the hands and feet, the first few sprayings are also applied only around the margin of the lesion, and as healing proceeds, islands of denuded epithelium are then separately sprayed.

Lewis and Morginson (1944), employing ethyl chloride in a series of 40 unselected cases in a general hospital in the United States, found that the agent effects immediate clinical improvement, with subsidence of vesicles and pustules, healing of denuded areas, increased dryness of the skin and regression of hyperhidrosis. Since recurrences were experienced in most of these cases within ten days after cessation of the ethyl chloride treatment, it was felt that the best use of the agent was as an adjunct to the customary management of these cases since it seems to produce an antagonistic environment for the fungi through promoting dryness of the skin.

PROPHYLAXIS

Where men are living under crowded conditions it is recommended that the Army-issue foot powder (see above) be applied to the feet and inside the footwear after a bath, or night and morning. The following powder, recommended by Goodman (1931), was also used satisfactorily by Prehn (1938):

Phenyl salicylate (salol)	gr. xl	2.5
Chloral hydrate	gr. xl	2.5
Purified infusorial earth (sterilized)	℥iv	120.0

For large-scale prophylaxis, as in gymnasiums, public showers, etc. it is usual to employ in a compulsory foot bath 20 per cent sodium hypochlorite diluted 20 to 1 and changed every second or third day. However, it would seem that as a result of experience in War II the Army has become very skeptical of the value of sodium hypochlorite solution for the prophylaxis of epidermophytosis.

Gould (1942) said that anywhere from a 3 to 10 per cent solution of sodium thiosulfate (the ordinary "hypo" of photographers) is just as satisfactory as the hypochlorite solution, but Warren (1943) inclined to the belief that any value sodium thiosulfate may have is likely due to its formation of copper salts upon standing in foot-bath containers made of copper; I take it there will probably be considerable argument upon this point.

The Surgeon General's Office has issued the statement (Bulletin U. S. Army Medical Department, 82, 19, 1944) that more progress will be made in the reduction of the disease through the thorough scrubbing of shower rooms and barrack floors and the exposure of flooring and duckboards to sunlight where practicable than through the forced employment of any sort of prophylactic foot-bath solution.

Actual fumigation of the shoes may be accomplished by inserting in them a piece of blotting paper containing a teaspoonful of formalin; the shoes are then to be wrapped up tightly in paper for twenty-four hours and are thereafter to be thoroughly aired for two days before being worn again. Birnbaum (1941) sprayed the formalin into the shoes with an ordinary atomizer on three successlve nights, not allowing them to be worn again until they had been aired for eight hours; I should not expect this method to be as efficient as the other. There is no need of destroying clothing since materials of all sorts may be sterilized safely by first washing in the usual manner, then soaking in a 1:1000 solution of bichloride of mercury for a day, and afterward thoroughly rinsing in water before drying.

POMPHOLYX

(*Dysidrosis*)

This is a well-known affliction of many individuals during the hot summer months; its exact relationship to sweating is not understood, but significantly the lesions occur principally on areas where perspiration takes place freely—the lateral aspects of the fingers and toes, and the palms and soles. Pearly vesicles appear embedded in the epidermis, there is much itching, and occasionally large bullae are formed and usually quickly ruptured by scratching. With the passage of the "hot spell," subsidence of the vesicular stage takes place but moderate desquamation and a yellowish-brown discoloration persist for several weeks. In the soles and palms the vesicles usually lie very deep and make their presence known principally through the "shotty" feel they give to these regions.

THERAPY

Pompholyx may appear in an individual having epidermophyton infection or seborrheic or other eczema, in which cases the treatment is merely that of the primary disturbance. In cases unassociated with other lesions and merely occurring when the individual sweats excessively, one should be very chary of applying the "strong" type of preparations used in epidermophytosis as they will often only aggravate these idiopathic cases. Indeed, it seems that the treatment most productive of results here is to do nothing and pray for cool weather.

RINGWORM OF THE SCALP

Ringworm attacks the scalp only in children. The patches are round and scaly, but not centrally involuted as in similar affections of the glabrous skin; they are not completely bald, but contain numerous brittle or broken hairs and dilated or "debris-stuffed" follicular orifices. In the older patches there are usually many young hairs with fine shafts. In severe cases the whole scalp may be involved and the itching becomes quite intense; a few instances of involvement of the eyebrows have been recorded.

THERAPY

Manual Epilation and Application of Antiseptics.—This, the old treatment of ringworm of the scalp, requires anywhere from six months to three years to bring about a cure except in the rare instances in which the infection is of "animal" origin (see below). The hair must be clipped short and maintained so, and the hairs in the affected areas plus those around the margins must be pulled out with the forceps. The scalp must be frequently and thoroughly washed with soap and water, and an antiseptic ointment, such as 10 per cent ammoniated mercury ointment, frequently applied over the surface (this ointment should be omitted, however, if iodine is to be applied later, unless it seems desirable deliberately to produce a dermatitis venenata). For application to the affected areas *per se*, the following are a few of the remedies used; they are all powerful irritants and are therefore to be employed with very great caution, especially as regards keeping them out of the eyes:

Chrysarobin	ʒj	4.0
Chloroform to make	℥ij	60.0

Careful!

Chrysarobin	ʒj	4.0
Petrolatum to make	℥ij	60.0

Careful!

Tincture of iodine	℥ss	15.0
Alcohol to make	℥ij	60.0

(Some men use the tincture undiluted.)

Iodine crystals	gr. x	0.6
Thymol crystals	gr. x	0.6
Oil of cinnamon	♏x	0.6
Petrolatum to make	℥ij	60.0

Crude coal tar	ʒiss	6.0
Zinc oxide	ʒiss	6.0
Petrolatum to make	℥ij	60.0

Resorcinol	ʒiss	6.0
Petrolatum (or glycerin) to make	℥ij	60.0

Whitfield 1 or 2 (see Epidermophytosis)

Salicylic acid	ʒj	4.0
Precipitated sulfur	ʒj	4.0
Petrolatum to make	℥ij	60.0

Betanaphthol	ʒij	8.0
Precipitated sulfur	ʒj	4.0
Petrolatum to make	℥ij	60.0

Salicylic acid	ʒiss	6.0
Gentian violet	gr. xviii	1.2
Alcohol to make	℥ii	60.0

X-Ray Epilation.—There is no longer any doubt that preliminary epilation of the entire scalp by the use of x-ray, to be followed by the application of the antiseptics as above, is the best available treatment; but Lewis and Hopper (1937) held that this method need not be resorted to if the infection is caused by fungi that are also pathogenic to animals (*i.e.*, chiefly *Microsporon lanosum* in contradistinction to *M. audouini*), and Levin and Behrman (1943) doubtless expressed the consensus in agreeing with this position. Wise said that in his extensive experience at the Vanderbilt Clinic the hair has come out in from seventeen to twenty-one days after x-ray epilation and regrowth has occurred within three months. However, I cannot refrain from cautioning the reader against placing his patient in the hands of just *any* upstart operator of an x-ray apparatus; this is a special technic, and, like all special technics, requires study and practice in order to obtain mastery. It is not easy to forget the unfortunate sequelae of unskilled roentgen ray or radium therapy.

RINGWORM OF THE BEARD

The treatment of ringworm of the bearded region differs in none of its essentials from the treatment of ringworm of the scalp.

SEBORRHEIC DERMATITIS

This is probably the commonest of all skin diseases. In the scalp it is known as dandruff, which may be of the dry scaly or the moist greasy variety. In many cases lesions are also seen along the fringe of hair on the forehead, in the eyebrows, on the outer aspects of the nostrils and behind the ears. The most frequent site of predilection other than the points mentioned is the sternal region; here the lesions are rounded, irregular, or circinate, and are covered with greasy yellowish scales. The differentiation between seborrheic dermatitis, ringworm of the glabrous skin and psoriasis is not always easy to make. There may be much itching.

THERAPY

The remedies for this condition are of course legion, which is simply an indication of the relative ineffectiveness of them all. However, any one of the following plans of treatment will lessen the severity of most cases; some will be "cured," though return of the lesions is almost certain. Many dermatologists feel that a fatty diet predisposes to this condition, and therefore rigorously restrict the intake of certain foods; I used to feel in a rather superior fashion that dieting for dandruff was too amusing to be taken with entire seriousness, but now, with the allergists almost daily enlarging their field, one can no longer be certain about anything. Other observers believe that a diet high in carbohydrate predisposes to this affection. Gross (1941) reported some very interesting studies of the effect of liver extract therapy in a group of cases showing seborrheic-like lesions but not the frank syndromes associated with deficiency in the various fractions of the vitamin B complex; he did not claim curative effect of liver extract in ordinary seborrheic dermatitis. The findings of Wright *et al.* (1943) indicated that if vitamin B complex therapy is to be of definite value, the pyridoxine (B_6) content must be adequate.

Ammoniated Mercury and Salicylic Acid.—These drugs, as in the following prescription, may be thoroughly rubbed into the scalp one or two nights a week, being washed out with soap and water the next morning. The reader should be warned that a few instances of severe idiosyncratic reactions to ammoniated mercury have been recorded.

Ammoniated mercury	gr. xlv	3.0
Salicylic acid	gr. x	0.6
White wax	ʒj	4.0
Hydrous wool fat	ʒv	20.0
Petrolatum to make	℥ij	60.0

This contains 5 per cent of ammoniated mercury and 1 per cent of the salicylic acid; the quantities may be doubled, giving 10 and 2 per cent respectively, but higher than this it is perhaps not advisable to go in the average case. On the nights when this ointment is not being used, Sutton advised the employment of the following lotion, which he accredits to Johnston:

Mercuric chloride	gr. ⅛	0.01
Chloral hydrate	ʒij	8.0
Spirit of formic acid (N.F. VII)	ʒiv	15.0
Castor oil	♏viij	0.5
Oil of bergamot to give odor		
Alcohol (80 per cent) to make	℥vi	180.0

Sulfur.—This drug may be used in the form of a simple sulfur ointment, as the following:

Precipitated sulfur	ʒj	4.0
White wax	ʒj	4.0
Hydrous wool fat	ʒv	20.0
Petrolatum to make	℥ij	60.0

or it may be somewhat reduced in amount and combined with salicylic acid, as in the following, in which the salicylic acid may be doubled in amount if considered desirable:

Precipitated sulfur	ʒss	2.0
Salicylic acid	gr. x	0.6
White wax	ʒj	4.0
Hydrous wool fat	ʒv	20.0
Petrolatum to make	℥ij	60.0

Resorcinol.—This drug is used either as ointment or lotion in the strength of 1 to 6 per cent; the following formulae, much used in my day at the New York Skin and Cancer Hospital, contain 4 and 6 per cent, respectively:

Resorcin	gr. xx	1.2
Petrolatum to make	℥j	30.0

Resorcin	ʒiv	15.0
Glycerin	℥j	30.0
Alcohol	ʒvj	24.0
Water to make	℥viij	250.0

Dark hair is not appreciably affected by resorcin, but the fact should be borne in mind that this drug will stain light, red, or white hair, especially if the patient exposes the head to the sunlight after its application. Resorcin monoacetate is said to be less apt to do so; it may be substituted for resorcin in equal amounts. A satisfactory prescription would be written by replacing the chloral hydrate in the Johnston formula (see preceding page) by ʒiiss (10.0 Gm.) of resorcin monoacetate.

SYCOSIS BARBAE

(*Barber's Itch*)

This is a chronic, discrete, pustular folliculitis of the bearded region, caused by several strains of staphylococci. The essential lesions are either superficial or deep-seated papules or pustules pierced by hairs that are easily pulled out. The infection may persist for many months or years, and the resultant alopecia and scarring are sometimes quite considerable.

THERAPY

Here, as in the ringworm infections, the area must be epilated either by x-ray or forceps, and the antiseptic and stimulating drugs applied in ointment or lotion for a long period of time. The reader is referred to the articles on ringworm of the scalp and beard, for I fail to follow the dermatologists in the fine distinctions they would have made in the treatment of the tineal and staphyl-

ococcic infections. X-ray is said to cure about 40 per cent of cases. Christie (1944) tried local applications of penicillin in 9 cases selected because of their failure to respond to ordinary methods of treatment over a long period of time; 7 were apparently cured after two or three weeks.

LICHEN PLANUS

This is an inflammatory disease of the skin that is usually subacute in its onset, though it tends to run a chronic course and to recur many times after spontaneous recovery or "cure." It is characterized by the appearance, principally on the flexor surfaces of the wrists and forearms and the inner aspects of the knees and thighs, of intensely itching, glistening, red to violaceous, round, angular or star-shaped, plane-topped, pinhead-sized papules; at first these tiny papules, many in number, remain discrete, but they tend ultimately to coalesce into rough scaly patches. The disease not infrequently attacks the visible mucous membranes; other rare forms there are with which we cannot be concerned in this book. Lichen planus is a dry disease throughout its course, with pigmented areas or slightly atrophic spots being sometimes left behind after departure of the lesions.

THERAPY

Despite the frequency with which this disease is seen in practice, very little advance in its treatment has been made in many years. Most observers feel that "cure" depends mainly on natural evolution and that treatment is therefore principally palliative. However, it is usual to treat the pruritus locally and to give preparations of arsenic and mercury by mouth (the organic arsenicals usually fail when injected) or bismuth by injection; Conrad (1942) favored the use of bismarsen. Mercury and bismuth administration are described in Syphilis, inorganic arsenic in Psoriasis and antipruritic measures at several places in the book (see Index). Some observers feel that the use of iron as in hypochromic anemia is of value especially when combined with the use of arsenic. Burgess (1941) employed preparations containing the vitamin B complex with some success in a small number of cases. In the most stubborn cases, x-ray is sometimes applied to the lesions, but with variable results; it seems to me that x-ray applied to the dorsal and lumbar vertebrae smacks a bit of hocus-pocus.

PSORIASIS

Psoriasis is a common, usually nonitching, nonpainful, inflammatory skin disease characterized by a typical course, a typical appearance and a typical distribution. *Course:* the disease usually develops between the ages of ten and thirty, persists for a variable period of time, disappears spontaneously, and recurs and disappears again many times throughout the patient's life. *Appearance:* the lesions are papular, multiform, dry, reddish, and covered with white, gray, or silvery imbricated scales. The scraping away of every one of the scales

from a single papule reveals a very red, easily bleeding elevation; in long-standing cases many of the papular lesions coalesce to form thickened patches covering surprisingly large portions of the body. In the intervals between attacks the skin usually clears entirely. *Distribution:* the eruption is symmetrical, and, from a beginning usually on the elbows and knees, may spread all over the body; the scalp is often involved, but the face and the backs of the hands are frequently spared even when the involvement elsewhere is very extensive.

Psoriasis is generally considered to be rare in the Orient and in the tropics, but Pardo-Castello (1934) said that it is of frequent occurrence in whites residing in Cuba, whose climate is subtropical. Most patients in the temperate zones are better in the summer and worse in the winter. The disease is extremely rare in full-blooded Negroes and American Indians. Nothing is known of its etiology or of what part, if any, heredity plays in its causation. In Lane and Crawford's (1937) series of 231 patients, about five times as many were overweight as were underweight—I wonder how this compares with the weight status of nonpsoriatic individuals in the same age groups? Treatment of psoriasis was probably described in the Papyrus Ebers, which was written about 1550 B.C.

THERAPY

While there are many cases of psoriasis that remain completely intractable ("an antidote for dermatologists' ego"—Bechet, 1936), the duration of the average moderately severe attack can usually be much lessened by proper local treatment. X-ray therapy sometimes causes temporary improvement, but the occasional good result would seem to be bought at an excessively high price; to wit: prolonged treatment, such as is necessary in this disease, practically always lowers the white blood count more than can be entirely safe; if it is unskillfully applied, the patient may be seriously burned; and the treatment may superimpose upon the lesions an itching, burning dermatitis. The use of autoserum, intravenous foreign protein, intramuscular injection of a suspension of the patient's own scales, low-protein diet, low-fat diet, lecithin feeding, lipocaic, venesection, autohemotherapy, x-ray stimulation of the thymus gland—all these measures have had their occasional successes, but I think that such results are utterly without significance in a disease so variable as this. The internal remedies recommended are legion, but the only one to which dermatologists return after their dallyings with other drugs—if they return at all—is arsenic. It is usually begun at 1 to 3 drops of Fowler's solution (U.S.P. solution of potassium arsenite) three times daily, and increased 1 drop per dose every other day until 10 drops are being taken after each meal; this dose is maintained for a week or ten days unless signs of slight poisoning supervene earlier, *i.e.*, puffiness under the eyes or about the ankles, or gastro-intestinal disturbances. It is not commonly realized that arsenical neuritis can also be produced with this method of administration. The best practice is perhaps to rest the patient for a while after he has been held the week or ten days on the full dose, but some practitioners gradually reduce the dose and thus bring him back again by gradations to a nonarsenical basis. There is nothing to indicate that any of the organic arsenicals have value here. Gold and manganese have both had a trial but one hears little of them nowadays. Of course the latest agents to have a vogue are the sulfonamides and vitamins, especially vitamins B, C, D and P (citrin); there have been some good results of course

because psoriasis is capricious and will respond at times to almost anything or again to nothing at all—witness Thurmon's (1942) report of beneficial effect in 62 per cent of 75 patients, and Saunders' (1944) report of favorable responses in 55 per cent of 27 patients, given sarsaparilla tablets. I think the most important recent report is that of Madden (1940), who treated 112 patients with the following agents: vitamin D, vitamin B_1, vitamin B complex, brewer's yeast, vitamin C, liver extract, diluted hydrochloric acid, estrogenic substance, sulfanilamide, bismuth salicylate, anterior pituitary extract or adrenal cortex extract alone or in combination with one another or in combination with a low-fat diet. No results which one could by any means call impressive came out of this study—Madden's treatment of choice remained a low-fat diet plus vitamin B, and some sort of exfoliating ointment.

A standard treatment is to send the patient south, but he is not likely to benefit greatly by a mere sojourn in a warm climate unless the body is freely exposed to the sun.

In the local treatment of psoriasis it is very essential that all the scales be removed before applying the remedial agent. This is usually accomplished by vigorous scrubbing with soap and water in a warm alkaline bath, but there are a few individuals who are made worse by the contact with water; for these, recourse must be had to the "grease bath," *i.e.*, the scrubbing of the body with some such preparation as the following, which is then to be thoroughly wiped off before applying the curative preparations:

Hydrous wool fat (lanolin)	℥v	20.0
Glycerite of boroglycerin	℥ij	60.0
Petrolatum to make	℥iv	120.0

The following preparations are perhaps those most used in treatment; the majority of cases will respond to any one of these, but in some cases the whole gamut will have to be run. All of these ointments should be worked into the lesions with a stiff toothbrush, but they are not to be applied to other than diseased areas.

Ammoniated Mercury and Salicylic Acid.—For treatment of the scalp and face a combination of these drugs is employed, as chrysarobin and the other irritants will ultimately get into the eyes when used as long as is necessary in psoriasis. The formula below contains 2 per cent of salicylic acid and 10 per cent of ammoniated mercury; the former may be increased gradually to 5 per cent and the latter very cautiously to 20 per cent; in rare instances both are carried much higher than this (warning: a few instances of severe idiosyncratic reaction to ammoniated mercury have been recorded):

Salicylic acid	gr. xl	2.4
Ammoniated mercury	ʒiij	12.0
White wax	ʒij	8.0
Hydrous wool fat	℥j ʒij	40.0
Petrolatum	℥iv	120.0

Chrysarobin in Ointment.—The drug is undoubtedly effective in more cases than is any other, but it is extremely disagreeable to use as it stains everything brown. The stains are only partially removed from linen by the use of a chlorinated lime solution. Also the drug may at any time, especially on the upper ranges of its effective concentration, produce a dermatitis that is sometimes very aggravating. It is usually begun at 5 per cent strength and

cautiously increased to 25 or even 35 per cent, though few cases will stand this latter concentration. The formula contains 5 per cent:

Chrysarobin	ʒiss	6.0
Petrolatum	℥ij	60.0
Hydrous wool fat to make	℥iv	120.0

Dioxyanthranol (*Anthralin*), introduced on the Continent a few years ago as cignolin, is chrysarobin minus a methyl group in the formula. It is reputed to be much stronger than chrysarobin; this may be employed as in the following formula:

Anthralin	0.1–1.0 per cent
Petrolatum to make.	

The advantages claimed for anthralin are that it does not have chrysarobin's propensity for causing kidney irritation upon being absorbed; that it does not cause extensive dermatitis and may be used on the face without causing conjunctivitis; and that it discolors neither the clothing nor hair so much as does chrysarobin. The indications are that this new drug is fully as effective as chrysarobin, but there have not as yet been published sufficient studies of it to make the point certain; in the concentration of from 0.1 to 1.0 per cent it may be substituted for chrysarobin in any of the following formulae.

Chrysarobin in Collodion, Gutta-Percha or Gelatin Film.—The drug may be prescribed in any one of these media to be painted on, a method more acceptable to the fastidious patient but less effective than the use in ointment; the gutta-percha formula is to be preferred, as chrysarobin is not soluble in collodion. The formulae contain 6 per cent, to be increased just as in the ointment:

Chrysarobin	ʒss	2.0
Collodion (not the flexible) to make	℥j	30.0

Chrysarobin	ʒss	2.0
Solution of gutta-percha (N.F. IV) to make	℥j	30.0

or the following may be written:

Chrysarobin	ʒij	8.0
Glycerogelatin (N.F. VII) to make	℥iv	120.0

Such a gel is melted and applied with a brush and covered with a bandage. Some physicians prefer the zinc oxide paste for vehicle:

Chrysarobin	ʒiss	6.0
Zinc oxide	℥j	30.0
Starch	℥j	30.0
Liquid petrolatum to make	℥iv	120.0

Tar.—The following are forms in which this substance is frequently applied:

Pine tar ointment (U.S.P. XII)	℥j	30.0
Petrolatum to make	℥iv	120.0

Oil of cade (Juniper Tar, U.S.P. XII)	℥j	30.0
White wax	ʒij	8.0
Hydrous wool fat	℥j ʒij	40.0
Petrolatum to make	℥iv	120.0

Chrysarobin, Tar and Salicylic Acid.—A compound sometimes successfully used during my time at the New York Skin and Cancer Hospital had the following formula:

Rectified oil of birch tar (N.F. VII)*	ʒiij	12.0
Salicylic acid	ʒvj	24.0
Chrysarobin	ʒvj	24.0
Anhydrous wool fat	℥j	30.0
Soft soap to make	℥iv	120.0

* In the interest of simplification of our armamentarium, I see no reason why this preparation, the beloved Oleum rusci of the dermatologists, could not in all instances be replaced by the oil of cade, a U.S.P. preparation from which it surely can differ only slightly, if at all, therapeutically.

Coal Tar.—Coal tar is often better borne than the wood tars; it may be substituted in any of the above formulae. Some dermatologists feel that recovery is hastened if ultraviolet radiation to the point of tanning is carried on in conjunction with the coal tar treatments. The lesions are wiped practically clean of the ointment and the light then directed onto the skin through a thin film of remaining ointment, the belief being that some new chemical substance, powerfully antipsoriatic, may be formed in the coal tar thus treated. Lesions are not re-treated with ointment until several hours after the daily light treatment.

Unna's Chrysarobin-Ichthyol Compound.—This much-used preparation is variously written, but I believe the following formula to be the one most often employed:

Chrysarobin	ʒiss	6.0
Salicylic acid	gr. xlv	3.0
Ichthyol	ʒiss	6.0
Petrolatum to make	℥iv	120.0

Resorcinol.—This drug is used in ointment in the strength of 5 to 10 per cent; the formula contains 5 per cent:

Resorcinol	ʒiss	6.0
Petrolatum	℥ij	60.0
Hydrous wool fat to make	℥iv	120.0

Pyrogallol (Pyrogallic Acid).—This drug is used in ointment in the strength of 5 to 10 per cent; the formula contains 5 per cent:

Pyrogallol	ʒiss	6.0
Petrolatum	℥ij	60.0
Hydrous wool fat to make	℥iv	120.0

Pyrogallol stains tissues and clothing black and is too irritating to employ about the eyes or genitalia. A greater objection to its use, however, is the fact that it may suddenly be absorbed in sufficient quantities to cause serious systemic poisoning; in rapid cases there are cyanosis, dyspnea, convulsions and collapse, but in the slower cases chills, diarrhea and vomiting, acute nephritis with dark scant urine, and sometimes jaundice and glycosuria, are the outstanding symptoms. The indications are to empty the gastro-intestinal tract with emetics and purgatives, apply heat to the body and stimulate; there is no specific antidote.

Betanaphthol.—This drug is probably less effective than pyrogallol, but it is also less dangerous; systemic poisoning of the phenol type may occur, how-

ever, from absorption through the skin, though the recorded cases are few. It is used in ointment in the strength of 5 to 10 per cent; the formula contains 10 per cent:

Betanaphthol	ʒiij	12.0
White wax	ʒij	8.0
Hydrous wool fat	℥j ʒij	40.0
Petrolatum to make	℥iv	120.0

or the following "peeling paste" may be applied for a short time twice a day:

Betanaphthol	ʒiss	6.0
Precipitated sulfur	℥j	30.0
Petrolatum	ʒiij	12.0
Soft soap to make	℥ij	60.0

LUPUS ERYTHEMATOSUS

Lupus erythematosus is a chronic inflammatory skin disease characterized by the insidious development of small, pink, dry, macular patches with grayish adherent scales; which patches, both by extension and coalescence, form well-defined, thickened areas, varying in size from a small coin to the palm of the hand or more, and having in their center one large or several small thin, colorless or whitish, atrophic scars with gaping follicular orifices. The sites of predilection of this disease are the scalp, the regions about the ears, the cheeks and the bridge of the nose; perhaps the next most frequent site is the back of the hands. The mucous membranes are involved in about one fourth of the cases. When the lesions occur on both cheeks with a connecting bridge across the nose, the most typical distribution of all, the "butterfly appearance" is often glibly referred to—an unfortunate designation, for certainly in the vast majority of cases these patches resemble no butterfly ever seen or heard of.

The etiology of this malady is entirely unknown. The cases usually begin between the fifteenth and thirtieth years and run an erratic course throughout the rest of the patient's life, though spontaneous disappearance sometimes occurs. There are no constitutional symptoms, and the patient's welfare is disturbed only insofar as the unsightliness of the affliction alters his or her environmental reactions. The acute disseminate variety of the disease, with its severe general symptoms and grave prognosis as to life, is too rare to concern us in this book.

SYSTEMIC THERAPY

It is said that rest is very valuable in the control of this disease. In acute exacerbations the patient must be protected from light, oftentimes to the extent of keeping him in total darkness for many days or even weeks. The fact that there are several types of systemic therapy indicates, I think, that there is dissatisfaction with them all.

Gold Salts.—At present in the United States, gold and sodium thiosulfate is the most extensively used gold preparation, though all those employed in Europe have their advocates here also. As with all new therapy, enthusiasm ran high in the beginning but it is now considerably abated. Schamberg and

Wright, who introduced gold and sodium thiosulfate treatment in this country, reported in 1936 on the results of their use of the drug intravenously in 76 patients during the preceding ten years. Of this number, 37 per cent were regarded as cured, 34 per cent greatly improved and 17 per cent moderately or slightly helped. Of those regarded as cured, 2 had been well with no relapse for seven years, 2 for six years, 2 for five years and 3 for four years. One or more relapses were suffered by 17 per cent of the patients after being partially or entirely free from lesions; some responded again to treatment, others were too discouraged to continue therapy. In Callaway and Stokes' (1938) series of 31 patients, 74 per cent suffered from one to four relapses after apparent cure. Stokes *et al.* (1944) agreed with many others that bismuth is equally as effective as gold and materially safer; in the Manual of Dermatology, prepared by Pillsbury *et al.* (1942) for the armed forces, it was explicitly stated that gold treatment should only be tried after it had been determined that bismuth was not effective.

Matters of dosage and reaction to the gold salts are discussed under Rheumatoid Arthritis (see Index).

Bismuth.—Pillsbury *et al.* (1942) recommended weekly injections of bismuth just as in syphilis, a course of at least eight weekly injections being necessary to determine whether or not the agent would be effective. As above stated, Stokes *et al.* (1944) valued bismuth more highly than gold; they stressed the nonspecific quality of the effect since in some instances arsenicals are effective where bismuth fails. Weiss *et al.* (1941) reported some success with the use of bismarsen in 28 cases.

Sulfonamides.—These drugs are being used of course and there is enthusiasm over the results in some quarters, but the fact that many failures as well as successes are being recorded indicates that as yet we know only that the long hoped-for specific in lupus erythematosus has not been found. According to Barber (1940) the reactions to sulfonamides are of frequent occurrence in this disease and of peculiar nature and violence. Pillsbury *et al.* (1942) did not recommend the sulfonamides in the Military Manual of Dermatology.

Quinine and Iodine.—The patient is given 7½ grains (0.5 Gm.) of quinine sulfate three times daily for five to seven days, during which time the lesions are painted with a tincture of iodine once each day; after a week, during which the crusts are removed either spontaneously or by poulticing, another course of treatment is given. Stokes *et al.* (1944), while not themselves endorsing this treatment, said that it is supported by a number of experienced observers; they said that the quinine should be pushed to at least 30 grains (2.0 Gm.) a day.

Liver Extract.—King and Hamilton (1941) were very pleased with the result of employing intramuscular injections of liver extract in 6 of their 8 patients. I have seen no further reports of the employment of this type of therapy.

LOCAL THERAPY

Pillsbury *et al.* (1942) made the point that ultraviolet irradiation or roentgen therapy should *never* be employed in this disease. Local destruction of small fixed lesions with solid carbon dioxide snow seems permissible, but as many failures as successes are recorded with this measure. I list below the agents most frequently employed locally but can only say that they have been found one and all to be sadly lacking in ability consistently to produce the kind of results that are occasionally reported following their use.

Sulfur.—This drug is usually applied once or twice daily in ointment; the formula contains 4 per cent, but it may be increased in strength:

Precipitated sulfur	gr. xx	1.2
Petrolatum to make	℥j	30.0

Sulfur and Salicylic Acid.—These drugs are used in combination to be applied in ointment once or twice daily, or alternated with the sulfur alone; the formula contains 4 per cent sulfur and 10 per cent salicylic acid, both of which may be gradually increased:

Precipitated sulfur	gr. xl	6.0
Salicylic acid	ʒiij	12.0
White wax	ʒij	8.0
Hydrous wool fat	℥j ʒij	40.0
Petrolatum to make	℥iv	120.0

Lotio Alba.—This is a mixture of sulfurated potash (U.S.P.) and zinc sulfate, usually applied once or twice daily. The following formula is for the mild form of the lotion, with which the treatment is usually begun; for a full description of the use of this *lotio alba*, see Acne.

Zinc sulfate	ʒij	8.0
Sulfurated potash	ʒij	8.0
Water to make	℥iv	120.0

Ichthyol (Ichthammol).—This drug is applied once or twice daily in ointment or collodion in 10 per cent strength.

Ichthyol	♏xlv	3.0
Petrolatum to make	℥j	30.0

or

Ichthyol	♏xlv	3.0
Collodion (not the flexible) to make	℥j	30.0

Phenol.—Pure liquid phenol is washed over the lesions once a week with a cotton applicator.

Phenol-Lactic Acid.—The following mixture is applied with a glass rod over the surface of the lesions once every ten days to two weeks: phenol, 1 part; lactic acid, 4 parts. The parts should first be cleansed with ether.

Trichloracetic Acid.—This substance is painted on the lesions with a cotton applicator once a week, the parts having first been cleansed with benzine to facilitate penetration.

Arsenic.—Equal parts of arsenic trioxide and acacia are made into a paste with a saturated solution of cocaine hydrochloride and spread over the diseased area, though no more than a square inch at a time should be treated. The paste is allowed to remain in place for twenty-four to forty-eight hours, when the slough is removed by poulticing.

Pyrogallol (Pyrogallic Acid).—This substance is applied in ointment to small areas twice a day for two or three weeks, the sloughs being removed from time to time by poulticing; the formula contains 20 per cent, but this strength is sometimes doubled:

Pyrogallol	ʒiss	6.0
Rosin cerate	ʒiv	15.0
Petrolatum to make	℥j	30.0

ECZEMA-DERMATITIS

There is a large group of maladies characterized histopathologically by an identical process of spongiosis. The occurrences are erythema, intercellular epidermal edema, microscopic and later macroscopic vesiculation, with or without the appearance of small isolated subvesicular papules. The lesions weep when the vesicles rupture and encrust when the high-fibrin exudate coagulates; scaling occurs if the keratinization process is much interfered with, and continued inflammation causes the skin to lose its elasticity and thicken with exaggeration of the normal lines (lichenification). Dermatologists are intensively seeking to simplify the very puzzling nomenclature of this group, but it seems to me that for the man in general practice who has had no specialized dermatologic training, the most profitable course is to consider any case in which the gross lesions more or less comply with the above description as one belonging in the "eczema-dermatitis" class. All such cases have an identical therapeutic approach; *i.e.*, each needs to be investigated from the standpoint of the "general considerations" presented below, and some will require the "local treatment" described further on.

THERAPY

General Considerations

The Metabolic and Endocrine Factors.—It is now apparent after a good many years of exhaustive and expensive research that there are no metabolic and endocrine disturbances underlying eczema-dermatitis with any significant regularity. Therefore routine blood chemistry and basal metabolic studies are probably not justified, nor is the routine administration of glandular products, or of calcium or any of the alteratives. Evidences are being found of local disturbances of metabolism in the skin but they are not such as can be determined by study of the general functions.

The Neurogenic Factor.—These dermatoses rarely heal in persons whose emotional apparatus is being often battered, for, as Sack pointed out a number of years ago, the skin occupies perhaps the largest single place in consciousness and has the widest and most varied sensory appeal and the richest vasomotor and other nerve supply in the body. Well does Stokes say, "A mycosis may even be influenced by the stock market, and eczema by a course in French."

The Allergic Factor in Adults.—The importance of allergy in the causation has come to be generally recognized; indeed, there are those who maintain that all cases are allergic in origin, but I think that not many observers are as yet willing to go that far. It is nevertheless certain that a most thorough search for the possible allergic factor should be made in every instance. Poison ivy, primrose, ragweed, hair and fur dyes, inks (the Sunday rotogravure section), face powders, and a host of other domestic and industrial substances are already convicted, as are also a number of foods. Sensitization studies are often very difficult and the manifestations quite fickle in these cases, at one time being present and at another time being absent, or sometimes being present but apparently without significant relationship to the symptoms. Possibly the allergic response goes up and down with the responsiveness of the sympathetic nervous system to fatigue and irritation, as Stokes asserts, so that a patient who cannot wear a certain fur jacket this season but can do so the

next may not be putting us to shame at all but rather showing conclusively how much the allergic state is bound up with other affairs; perhaps our perky Miss by flaunting her coat flouts those stubborn fellows only who will see merely the immunologic phases of the subject.

The reader must turn back and study the subject of allergy, its detection and methods of treatment. The dermatologic phases are being particularly well presented by Sulzberger; the especially interested reader is referred also to the review of Stokes and Garner—see Bibliography for a list of all these papers. The usual injection methods of desensitization have upon the whole been disappointing in the skin cases; the withholding of convicted foods is much more often rewarded by instant improvement.

The Feeding Problem in Infants.—In the approach to the very distressing matter of infantile eczema-dermatitis not a great deal of progress has been made. A few babies with mushy, odorous ("pig-pen") stools and a pronounced blue reaction to the iodine test will improve when the starches are greatly restricted, and the ones with acid, green, loose stools will be helped by sugar restriction, but why eczema should be associated with such digestive disturbances, and be relieved when they are corrected, is far from clear. In the vast majority of cases there is no such association and it is here that one might expect the allergic approach to be the most profitable. However, many allergists feel that intracutaneous or scratch tests do not offer a very accurate index of clinical sensitivity, for oftentimes identification of the offending substance is not followed by cure of the attack when the substance is withdrawn, or the patient may give a negative test—for example, to cow's milk—and clear up nevertheless when this article is removed from the diet. Some allergists feel that so far as foods are concerned the only thing of value is the ingestion test; Cooke (1944) would include the patch test with what he calls the "clinical test by trial and error," but he admitted that he had had very little diagnostic success in his clinic. However, in some instances there seems to be such pronounced relationship between food sensitivity and eczema that the mere presence of the food substance in the environment of the infant, even without ingestion, will be productive of violent symptoms; Horesh (1943) reported 9 cases in which symptoms were provoked by inhalation of the vapors or odors from the convicted food, either cooked or raw.

Many vegetable substitutes for milk have been employed, such as coconut, soy bean, poppyseed, taro. The one with which most experience has been had is that known as Sobee, a mixture of soy bean flour, barley flour, olive oil, sodium chloride and calcium carbonate, introduced by Hill and Stuart in 1929. This mixture contains adequate amounts of the necessary minerals and of vitamin B but must be supplemented by orange juice and cod liver oil for the other vitamins. Six level tablespoonfuls of this food are usually added to 7 ounces of water, and unless the stools are loose a level tablespoonful of dextrimaltose is also added. An occasional infant, however, is also sensitive to this soy bean milk, and Hill (1941) also found that a great disadvantage of the preparation in some instances is that it causes large loose bowel movements and irritated buttocks. Glaser (1944) is studying the use of strained meats as a protein basis for milk substitutes and his work will certainly be worth watching.

Many pediatricians have observed that the boiling of milk for four to six hours, the prolonged boiling of all foods, or the substitution of evaporated or dried milk are often helpful measures. However, Rattner (1935) pointed out

that not all evaporated milks are subjected to the requisite amount of heat in their processing, and he therefore advocated the vigorous boiling of evaporated milk for several minutes before use. Vitamin C in the form of fruit juices is required to supplement boiled milk. A standard brand of evaporated goat's milk is also used with advantage occasionally.

Desensitization to milk was attempted by Rattner, beginning with doses of cow's milk of a drop or less daily by mouth and increasing the quantity so slowly that normal amounts would not be reached until six to nine months had passed. Individuals thus desensitized are said to require to take milk continuously throughout their lives to retain the immunity.

Human Dander in Infantile Eczema.—Simon (1944) stated his belief that human dander is important as a cause of eczema in infants and young children, offering the following evidence: (*a*) positive skin reactions to the patch test with human dander in 15 of 20 infants and young children with eczema and only one positive reaction in 23 noneczematous infants and children (might one question these dander patch tests on the basis of histamine content?); (*b*) the fact that all children are exposed to their own dander or that of others; (*c*) prompt clinical improvement in 3 of 4 cases following the institution of measures directed at avoidance of contact with human dander; (*d*) reproduction of the lesions at will in 4 cases (out of four attempts) on a previously uninvolved skin area by exposure of this area to contact with human dander. If these findings can be confirmed it would certainly seem that a major contribution has been made by Simon.

Focal and Secondary Infection as a Factor.—It is a definite clinical impression that a focus of infection somewhere in the body has a very deleterious influence on eczema-dermatitis. Obviously, every effort should be made to eradicate foci, but bearing in mind the "high-strung" nature of many of these patients, the pursuit of the elusive foe must be made with the utmost calmness and even leisure. In some instances a secondary disease engrafted upon the primary may be the more serious of the two, as was the case in instances reported by Wenner (1944) in which infantile eczema was complicated by the virus of herpes simplex. Boisvert and Powers (1944) said that when a child has eczema and streptococcal fever concomitantly it is likely that the skin lesions will become endogenously infected with hemolytic streptococci. In such instances treatment of the skin lesions with sulfathiazole ointment is often effective but one must always weigh the danger of inducing sulfonamide sensitivity in this way and thus prohibiting subsequent use of the drug when it is urgently needed as a life-saving agent.

Types of Skin.—The person with the dry, ichthyotic, parchment-like skin will be better in summer or in warm climates because of the increased sweating, but the prognosis in him is unfavorable for the reason that his type of skin is definitely hereditary and so he begins his eczema-dermatitis career with a tendency which is incurable. He needs to avoid soap and to use greases plentifully, tends to become easily infected, and should probably not be given roentgen therapy, "which makes a bad matter worse by causing glandular atrophy." In the opposite type, the person with an oily, seborrheic tendency, Stokes feels that there is a definite indication for reduction of carbohydrates in the dietary, since the process is probably closely bound up with the carbohydrate storage mechanism and metabolism in the skin. In these cases the scalp, which is always concerned in the seborrheic process, must be treated; sulfur will be found to be almost specific when properly used; and there is a

definite indication for the use of the roentgen ray to reduce the activity of the sebaceous glands. Prognosis is better than in the ichthyotic type.

A good ointment for use after the bath by persons with excessively dry skin is the following:

Hydrous wool fat	℥v	20.0
Glycerite of boroglycerin	℥ij	60.0
Petrolatum to make	℥iv	120.0

As a substitute for soap, Lane and Blank (1941) offered a mixture which I present in prescription form below:

℞	Sulfonated olive oil	℥ij	60.0
	Sulfonated teaseed oil	℥ij	60.0
	Liquid petrolatum	℥iv	120.0
	Water to make	Oj	500.0
	Label: Use as soap substitute.		

Pyogenic and Mycotic Factors.—Pustular complications point to the necessity to employ mild wet antiseptic dressings and later ammoniated mercury ointment, beginning with not above 1 or 2 per cent concentration. X-rays are to be used cautiously but ultraviolet radiation may be of some value. Those who are investigating the metabolism of the skin feel that here also the carbohydrate intake should be reduced. With regard to the mycotic factor, it can only be said that undoubtedly many cases of so-called "epidermophytosis" are really eczema-dermatitis, and conversely that some cases of eczema-dermatitis have a mycotic factor which is uppermost. Certainly many cases of epidermophytosis that are resistant to the ordinary treatment will be found upon careful restudy to have become eczematous, particularly beyond the borders of the original mycotic infection, and are being aggravated perhaps by the application of strong keratolytics.

Local Treatment

Early Stage.—In the vesicular stage the use of wet dressings is the method of choice. They should not be applied with an occlusive covering, such as oiled silk or paper, but in such way as to gain the additional soothing and antipruritic effect of evaporation. Potassium permanganate is acceptably used as follows:

Potassium permanganate (1 tablet)	gr. v	0.3
Water to make	3 quarts	3000.0
This is an approximately 1 : 9000 solution.		

Of course saturated solution of boric acid may also be used, but the permanganate solution is not apt to become excessively irritating if inadvertently allowed to dry, as the boric acid may occasionally do. Lead and aluminum acetates are also much used because they are astringent and tend to lessen exudation, and are also to some extent antipruritic, but they are often too irritating to be borne by acutely inflamed tissues. The diluted solution of lead subacetate of the N.F. was deleted from the U.S.P. because too weak for most purposes; it is best to write for the N.F. solution of lead subacetate and direct the patient to dilute it with 10 to 20 parts of water. Burow's solution, the solution of aluminum acetate (N.F.), is to be diluted with 5 to 10 parts of water. Full strength alcohol is sometimes employed for wet dressings where there are no open lesions.

In excessively itching cases the alkaline colloid bath is often helpful. Fill the tub half full with water just at body temperature, add a cupful of sodium bicarbonate, and then place in a cheesecloth bag 3 cupfuls of previously boiled oatmeal, and squeeze it in the bath until the water becomes opalescent. Such baths may be taken for ten to twenty minutes several times daily. Afterward the patient is to be patted dry and may have a boric acid, or the official rose water, ointment lightly applied; or the body may be powdered. In some patients, 1 quart (1 liter) of vinegar to the tub of water has antipruritic effect.

Some patients do not bear wet dressings well and must be treated with such lotions as will coat the lesions, or perhaps even with powders. The N.F. calamine lotion coats well but will crust if allowed to dry too much between applications; it is to be removed with sweet oil, not water, or with the oil and egg-yolk method of Glaze: thoroughly and gently work oil into the skin and then add a small quantity of egg yolk (one yolk will serve for twenty or thirty cleansings if used economically), and briskly work up an emulsion; the addition of a few drops of water helps. Rinse in cool water. In some patients the amount of inert powder in the calamine lotion makes it too drying and irritating, but they will often find a mixture of the lotion and sweet oil in equal parts very soothing.

Prepared calamine	℥j ʒiiss	40.0
Zinc oxide	℥j ʒiiss	40.0
Glycerin	ʒiiss	10.0
Magma of bentonite	℥vi ʒv	200.0
Solution of calcium hydroxide to make	Oj	500.0

A simple powder for dusting on dry or wet lesions is the following.

Boric acid	ʒij	8.0
Zinc oxide	℥j ʒiiss	40.0
Talcum to make	℥iv	120.0

The substitution of salicylic acid for the boric acid, in equal quantity, will make the powder antiseptic, but of course such a mixture must be used with extreme caution on acutely inflamed lesions. A menthol-boric acid combination, with talcum to make it stick, is often remarkably antipruritic:

Menthol	gr. xl	2.5
Boric acid	℥ij	60.0
Talcum to make	℥iv	120.0

Sometimes before using such a powder it is of advantage to sponge the affected area with hot sodium bicarbonate solution and then apply the powder after merely mopping off the solution.

For more active antipruritic effect, 1 to 2 per cent each of phenol and menthol may be added to the calamine lotion, but of course open or very acutely inflamed lesions contraindicate this application.

In some acute cases, particularly of infantile eczema-dermatitis, White's crude coal tar ointment may be used from the very beginning, taking care that the preparation is made according to the corrected formula, and that a properly prepared tar is used:

Crude coal tar	ʒss	2.0
Zinc oxide	ʒss	2.0
Petrolatum	℥j	30.0

Since the above preparation is often removed from the surface of the body with great difficulty, Downing *et al.* (1944) suggested as a substitute for the petrolatum a special base consisting of 5 per cent of diglycol stearate and 95 per cent of petrolatum prepared by fusing these two substances together and stirring the product until it is congealed. Crude coal tar is often used full strength as a paint, particularly for application to the cheeks and the resistant lesions behind the ears.

In cases of infantile eczema it is nearly always necessary to resort to forceful prevention of scratching, either through tying the wrists and ankles loosely to the sides of the crib or resorting to the employment of splints. A light masturbation splint, applied just above the knees, will effectively prevent rubbing with the feet. Wool should not come in contact with the body, and in some cases it is best to dress only in a diaper in a draped crib with an electric bulb to keep it warm. Pilcher wrote as follows of epinephrine to relieve the excessive itching: "The hypodermic dose was from 0.1 to 0.3 cc. of the 1:1000 solution, seldom more than 0.2 cc., however. This is somewhat large in comparison with the usual adult dose, but harmful effects were not seen. Occasionally pallor of the face and extremities (from vasoconstriction) was noted, of but a few minutes' duration without other signs of toxicity. It is my impression that the relatively large dose is necessary for effective results. The infants varied somewhat in their reaction to epinephrine; for instance, one of 9 Kg. weight was relieved of its suffering with 0.15 cc. and became quite pale with 0.2 cc., while a 5.5 Kg. infant of about the same age required 0.2 cc. for results and showed pallor only with 0.3 cc. The relief is usually striking, is noted promptly, often within two minutes, just as it is in urticaria, and may persist for an hour or more, and not infrequently the patient falls into a restful sleep."

Subacute Stage.—After the more acute symptoms have subsided, the use of creamy pastes and salves may be begun, either for protection from clothing and dirt in the milder cases, or to tide over the period of subsiding inflammation in those cases in which it is apparent that the use of stronger stimulating and keratolytic agents will be later necessary. They are spread over the lesions like butter. Unna's soft zinc paste is much used:

Zinc oxide	℥j	30.0
Precipitated calcium carbonate	℥j	30.0
Linseed oil	℥j	30.0
Solution of calcium hydroxide	℥j	30.0

Lassar's zinc paste has a small amount of salicylic acid (2 per cent), which is slightly stimulating, and it is of such consistency that, if hydrous wool fat is substituted for half the petrolatum, a liberal dusting with talcum powder will form a crust on top of the application that requires little further protection from the clothing.

Salicylic acid	gr. xl	2.5
Zinc oxide	℥j	30.0
Starch	℥j	30.0
Petrolatum	℥ij	60.0

Another well-known paste is that of Boeck:

Glycerin	ʒiij	12.0
Starch	ʒvj	24.0
Talcum	ʒvj	24.0
Solution of lead subacetate to make	℥iv	120.0

Some observers of large experience like to use ichthyol (ichthammol) in this stage; Becker (1931) favored the following:

Ichthyol	ʒj	4.0
Zinc oxide	ʒj	30.0
Petrolatum to make	℥iv	120.0

In using any of these pastes or salves, water should not be employed for their removal; use sweet oil, or the method of Glaze (described in the beginning of the section on local treatment).

Chronic Stage.—Before applying any of the stimulating and keratolytic agents in effective strength, it is good practice to try out the sensitiveness of the skin with a very mild stimulant; for instance, the ichthyol-zinc paste above, or one can proceed to the use of salicylic acid and the tars by first applying the following, in which each of the active ingredients is present only to the extent of 0.5 per cent (therefore, doubling these two figures would give 1 per cent, tripling 1.5 per cent, quadrupling 2 per cent, etc.):

Salicylic acid	gr. iiss	0.15
Pine tar	gr. iiss	0.15
Zinc oxide	ʒij	8.00
Petrolatum to make	℥j	30.00

The best of the available tar preparations are pine tar, coal tar and juniper tar (oil of cade). For any of them dosage must be determined in each individual case; as previously stated, coal tar is often surprisingly well borne in high concentration. Juniper tar has perhaps the least unpleasant odor, but all of the tars are nasty messes. The prescription containing tar a few pages back is a satisfactory basic one for coal tar therapy, or any of the tars may be combined with salicylic acid, as in the prescription just given. Perhaps it is of some value to know that the wood tars are acid in reaction and coal tar alkaline.

Sulfur may also be used in any proportion if the patient's tolerance is first carefully tested; the seborrheic greasy type will bear it best and derive the most benefit from it. In the following, 3 per cent is combined with 1 per cent of salicylic acid, and an ointment instead of paste base is used.

Precipitated sulfur	ʒss	2.0
Salicylic acid	gr. x	0.6
White wax	ʒj	4.0
Hydrous wool fat	ʒv	20.0
Petrolatum to make	℥ij	60.0

If greater cerate-like consistency is desired, paraffin may replace the wool fat and be increased up to 50 per cent.

Resorcinol concentration must also be gauged by each patient's individual reaction; it is best perhaps to begin with 1 or 2 per cent, but less than 5 per cent is rarely effective on thickened areas; it is occasionally carried up to 20 per cent. The formula contains 5 per cent:

Resorcinol	gr. xlv	3.0
White wax	ʒj	4.0
Hydrous wool fat	ʒv	20.0
Petrolatum to make	℥ij	60.0

For more prolonged application, the paste base would be substituted.

Ammoniated mercury is also very useful at times; in the following, 5 per cent is combined with 20 per cent of the liquid tar preparation of the N.F.:

Ammoniated mercury	gr. xlv	3.0
Solution of coal tar	ʒiij	12.0
Hydrous wool fat	℥j	30.0
Petrolatum to make	℥ij	60.0

There is twice as much wool fat as petrolatum here because of the necessity to incorporate the large amount of fluid; the anhydrous fat would be even better.

Local treatment of some sort is necessary in practically all cases of eczema-dermatitis, but it is by no means certain that in a given case the same preparation will be serviceable for all lesions. At times acute weeping areas on one portion of the body will demand wet dressings while lichenified areas elsewhere are being treated with the tars, salicylic acid, and so on. Utmost co-operation on the part of the patient is of prime importance.

Special Antidotal Measures in Ivy Poisoning

Ivy poisoning is a serious matter and I do not feel warranted in omitting the special measures which have been employed in combating it, but as a result of an attempted evaluation of such measures, Howell (1943) concluded that under the circumstances in which they are likely to be employed, practically none of these measures has worked; indeed, the fact that so many agents are listed below would tend strongly to indicate that none of them are very reliable.

Soap and Water.—The vesicles and bullae should be punctured and drained and the parts then thoroughly washed with soap (generous lather) and water. In washing and rinsing it is important to bear in mind that the object is to get rid of the irritant, therefore the soaping and rinsing must be done in the direction away from the unaffected parts; *i.e.*, wash from the elbows down toward the hands and rinse in the same way. If the area is then rinsed or wiped over with alcohol, which is a solvent for the poison, this too must be done in the direction away from the unaffected skin. Gasoline also is a solvent to be used in the same way.

Lead.—Lead preparations, such as the lead and opium wash of the N.F. (lead acetate, 18 Gm., tincture of opium, 35 cc., water to make 1000 cc.), are not so popular now as formerly; at best they merely precipitate the poison, which must then be washed away.

Sodium Sulfite and Phenol.—Sutton says that a saturated solution of sodium sulfite, to which 0.5 per cent phenol has been added, has served him well; the following should be written:

Exsiccated sodium sulfite (U.S.P. IX)	℥viij	250.0
Phenol	ʒj gr. xv	5.0
Water to make	Oij	1000.0

Formaldehyde and Phenol.—Hessler has satisfactorily used formaldehyde and phenol; he writes: "My usual formula is: solution of formaldehyde (formalin), 5 cc.; saturated aqueous solution of phenol (1:15), 10 cc.; distilled water to make 100 cc. (to this may be added a drop of methylene blue solution, as blue is a color that leads people to pause about using internally. To disguise the phenol odor, to which some object, a drop of some essential oil may be added). In dispensing I supply a 4-drachm vial with a swab in the

cork and with the directions: Apply freely the first time; after that use sparingly every few hours as needed. . . . The hardening and tanning effect of formaldehyde must be considered and explained to patients. The earlier the solution is applied, the better the effect."

Zinc Sulfate.—Irving writes enthusiastically of the use of zinc sulfate: "All irritation and even eruption can be prevented if it is used immediately after exposure. If used within twenty-four hours after exposure or ten hours after the appearance of the vesicles, it will abort the attack. If the case is not seen until the deeper layers of the epidermis are involved, the cure is slower but just as sure. To abort an attack, use 10 grains (0.6 Gm.) of zinc sulfate to 1 ounce (30 cc.) of water. For later treatment, use half strength."

Ferric Chloride and Paraffin.—McNair championed ferric chloride and paraffin. "The effect of ivy poisoning is much like that of a burn, and the treatment suggested resembles that used successfully during the war in burn cases. The affected parts are first bathed with ferric chloride solution, to neutralize the poison. The skin is dried and melted paraffin is painted over it. A thin sheet of cotton is laid over the wound, and this also is covered with paraffin. The affected area is thus protected from air and from rubbing, and new skin is given a chance to grow." The paraffin may also be swabbed on, as is often done upon the face. This treatment has periods of popularity, but one should not overlook Traub and Tennen's (1936) report of 2 cases of permanent pigmentation caused by it; Reyner (1939) also reported such a case which, however, was said to have responded to ultraviolet irradiation.

Benzoyl Peroxide.—Lamson stated that very great relief follows upon the application to the lesions of benzoyl peroxide as a dusting powder in a considerable proportion of cases, but pointed out the inadvisability of using the substance in this form because of its high inflammability and explosiveness. A paste made from the powder and a lubricating jelly containing glycerin is said by him to be just about as effective and to be nonexplosive and no more inflammable than a bandage.

Tannic Acid.—Schwartz and Warren (1941) reported the successful use of this agent in a small number of cases: vesicles are clipped open with sterile scissors, or the smaller ones rubbed open with alcohol-saturated gauze, and a dressing soaked in 10 per cent tannic acid solution applied for one-half hour once daily.

Collodion.—Woodward (1940) reported that painting collodion over the affected sites brings instantaneous relief.

Sodium Perborate "Protective" Ointment.—Schwartz *et al.* (1940) reported that application of the following ointment affords protection to those exposed to poison ivy: stearic acid (triple pressed) 200 Gm., potassium hydroxide (sticks) 14 Gm., alcohol (90 per cent) 40 cc., water 800 cc. In Shelmire's (1941) hands this ointment was no more protective than calamine or zinc oxide in vanishing cream, zinc oxide ointment or plain petrolatum, all of which offer only slight mechanical protection. Howell (1943) also found sodium perborate unsatisfactory under experimental conditions.

Potassium Permanganate.—Howell (1943) found in experimental studies that the liberal application of 10 per cent potassium permanganate solution decreased the severity but did not prevent the eruption in less sensitive subjects, but in highly sensitive subjects it was not effective. Pillsbury *et al.* (1942) also stated that the application of potassium permanganate soaks is the best first approach.

Whole Blood Injections.—Grimes (1931) reported a series of 20 cases in which 10 cc. of the patient's own blood was drawn from a vein and immediately reinjected into the gluteal region; the symptoms disappeared so rapidly that he suggested some sort of specific action. I have seen no further report of the use of this method.

BOILS

(*Furunculosis*)

Boils are acute, deep-seated, circumscribed inflammations of sebaceous glands or hair follicles; the causative organism is probably a staphylococcus in most instances. In the beginning the skin is smooth, tense and red, but in a few days the head of the elevation either becomes pustular or the whole mass becomes boggy; at this point the boil either discharges its pus and necrotic tissue or retrogresses without rupture. There may be a great many boils present at one time on various portions of the body surface, and in some cases new "crops" continue to appear for many months. The individual lesions are very painful and the patient is extremely uncomfortable, but the malady is seldom dangerous to life except in the diabetic or nephritic, or if the boils are on the face or upper lip. Of course, a crop of boils superimposed upon an acute infectious disease is a very serious matter.

THERAPY

General Measures.—The individual suffering from this affliction should be given a complete physical examination, during which the discovery of some debilitating constitutional disease may furnish the key to the therapy. The elimination of demonstrable foci of infection has sometimes been followed by rapid improvement, but by no means regularly. "Specific" immunization with stock or autogenous vaccines has been going on for a long time now and has as yet very little to its credit. Bacteriophage has almost completely failed here as in most other diseases.

The drugs used internally in the attempt to put a stop to the attack are legion, which probably means that none of them is consistently of value. I therefore set down here only those prescriptions that I believe to be most often employed—as to the rationale of their use, perhaps the least said the better.

Rumex mixture:

℞	Potassium acetate	ʒvj	24.0
	Tincture nux vomica	ʒij	8.0
	Fluidextract of rumex to make	ʒiv	120.0

Label: 1 teaspoonful after meals.

or

Startin's mixture:

℞	Ferrous sulfate	ʒj	4.0
	Dilute sulfuric acid (U.S.P.)	ʒiv	15.0
	Magnesium sulfate	℥j	30.0
	Syrup of ginger	℥j	30.0
	Water to make	℥iv	120.0

Label: 1 teaspoonful after meals and upon retiring, or 4 teaspoonfuls before breakfast.

or

℞ Dilute sulfuric acid (U.S.P.) ..... ʒiij 90.0
Label: 20 drops in water after meals.

or

℞ Calcium sulfide ..... gr. vj 0.4
Lactose sufficient to make 24 capsules.
Label: 1 capsule after meals and upon retiring.

Ewell (1935) reported that intravenous injections of neoarsphenamine at five-day intervals served himself and associates very well. There are of course reports of the successful employment of the sulfonamides, particularly sulfathiazole, but I think it significant that none of them has appeared recently. Coleman and Sako (1944) observed the rapid disappearance of multiple furuncles in 6 children under penicillin therapy. Barnes (1943) reported 16 patients each of whom had a low basal metabolic rate or basal temperature; further lesions did not develop in any of these individuals after the institution of thyroid therapy as in the treatment of myxedema but they did recur when the medication was discontinued.

Irradiation.—There are many enthusiastic reports of the results of x-ray therapy, but I like always to remember what sanguine and optimistic fellows the roentgenologists are. Still, Fink (1941), of the University of Minnesota Hospitals, reported that 25 of 30 treated patients were definitely and quickly relieved, and that is of course something. Ultrashort-wave diathermy was having a great vogue a few years ago; it seems to me one does not hear it mentioned in this connection quite so often nowadays.

Local Treatment.—I do not believe that there is any known substance that will bring about the regression of a lesion once it has begun to develop, but Price (1944) stated that in several instances he thought he had put a stop to the attack of boils in 11 patients in whom he thoroughly washed the area on which the boils had been appearing for twenty to thirty minutes with 70 per cent alcohol during a period in which there were no boils present. To hasten maturation, in order that the contents may be evacuated spontaneously or with the aid of the knife, hot compresses are sometimes of value, though it is often very difficult to accelerate the pace of a boil's development. Certainly linseed or any other kind of special poultice (honey, sugar, bacon, bread and milk, or the whatnots of household medicine) has no advantage over plain water beyond the requiring of less attention after it is applied, but the addition of an antiseptic, such as 1 teaspoonful of compound cresol solution to the pint of water, is of value in protecting the surrounding skin. To make a linseed poultice, add 1 part linseed meal with constant stirring to about 3 parts of boiling water to make a thin dough; spread about ½ inch thick on cloth and fold the edges to prevent escape; cover with oiled silk and cotton after applying. The poultice may be reheated as often as needed.

The body should be kept absolutely clean by a daily bath with hot water and soap; 4 ounces (120 Gm.) of boric acid may be added to the small tub of water. It is well after the bath to pat the body dry with a clean towel rather than to rub it, a procedure that will lessen the liability of the infection to spread by contact, and also protect any small pimples that might be present from abrasion and consequent greater liability to infection. Underclothing and bedclothing should be changed daily.

Incision.—It is usual practice to freeze the skin over the boil with ethyl chloride before incising, but all of us know that the resulting anesthesia is far from satisfactory. Mabry (1937) evolved the following improvement in technic

as a result of having been himself afflicted with a series of boils: "The furuncle is frozen as has always been done. A towel clamp now grasps the frozen skin and lifts it up or away from the body while the knife makes pressure inward. The inward pressure of the knife becomes a balancing or counteractive force against the towel hook. This prevents the deep pressure being made over the hard, inflamed hypersensitive mass and eliminates the pain, because the pain has always been caused by the knife pressure on the indurated mass and not by the cutting."

ACNE

Acne is an inflammatory skin disease symmetrically involving the face; sometimes, also, the interscapular or sternal regions are involved, and occasionally the whole back. The skin is greasy, contains many blackheads (comedones), and the acne lesions, which are at first papular, then become pustular, and finally dry up with more or less crusting. The essential process in the disease is a functional overactivity of the sebaceous glands, combined with a follicular hyperkeratosis; upon this is superimposed pustulation, and, at times, deep-seated granulomatous infiltration. Neither the so-called "acne bacillus" nor any other organism is any longer believed to be of primary etiologic importance. Acne being essentially a disease of adolescence, there is every reason for suspecting that an endocrine imbalance lies at the root of the matter, but proof of the fact is not yet at hand. The first appearance of the disease in an individual past twenty-five should cause the physician to inquire into the occupation (tar, oils, paraffin, chlorine), search for foci of infection and question regarding the use of goiter preventives.

The consensus is that the ingestion of iodine, even in the small amounts contained in iodized table salt, causes an increase in the number and severity of the lesions, but there are a few men of experience who disagree with this opinion. Bingham and Macke (1944) found that acne often became a very distressing disease in Navy personnel under tropical conditions during War II. It is said that the malady is of rare occurrence among such primitive peoples as the Eskimos, native black Africans, Australian aborigines and Maoris, but that as these people adopt modern methods of living the condition occurs more frequently.

THERAPY

General Measures.—The acne patient should be given a thorough physical examination, and especially should a careful history of past ailments be taken, for the elimination of chronic foci of infection has occasionally been rewarded by rapid improvement. Usually, however, the malady responds all too slowly to any type of treatment. Here, as everywhere else, I am opposed to the routine employment of drugs "to keep the bowels open" unless constipation is actually shown to exist—and even then cathartics are rarely indicated (see Colon Consciousness). Startin's mixture is used in nearly every case at some time; very likely it has no more value than accrues from giving the patient something to take from a bottle.

There is certainly less belief today than there was a few years ago in the excessive use of carbohydrates, especially "sweets," as important in prolonging the siege; Crawford and Swartz (1936), who deliberately maintained pa-

tients on a high carbohydrate regimen, failed to find the diet in the least harmful. LeWinn and Zugerman (1942) found fat tolerance to be normal in their 20 patients. Wortis (1937) reported great improvement of the acne in 6 patients undergoing hypoglycemic insulin treatment of psychoses; Semon and Hermann (1940) also reported improvement in all of their 13 patients in whom insulin was used primarily to combat acne; but let us go slowly here for insulin is not an agent to play with lightly and certainly much harm would be done if word began to go around about the "insulin cure for acne." Cormia (1940) was able to detect clinical evidence of food sensitivity in 20 per cent of his 32 patients, most of whom were helped by food eliminations. There is no evidence as yet showing any of the endocrine products to be of proved worth though there is a considerable stir of investigation at the present time in this very tempting field. The vitamins likewise have no very impressive list of consistent successes to their credit. What has been said of vaccine therapy in furunculosis will apply equally well here in acne. Yeast should certainly be left to the quacks.

Startin's mixture:

℞	Ferrous sulfate	ʒj	4.0
	Dilute sulfuric acid (U.S.P.)	ʒiv	15.0
	Magnesium sulfate	℥j	30.0
	Syrup of ginger	℥j	30.0
	Water to make	℥iv	120.0

Label: 1 teaspoonful after meals and upon retiring, or 4 teaspoonfuls before breakfast.

Local Treatment.—The things necessary are to get rid of the blackheads, cleanse and disinfect the skin as much as possible and apply a keratolytic agent. The face should be bathed in hot water until it becomes quite red, the blackheads pinched out, or preferably removed with an extractor, all abscesses incised and drained, the face again bathed in hot water to which 1 teaspoonful of the compound solution of cresol has been added to the pint, and then the keratolytic should be applied. At the New York Skin and Cancer Hospital it was formerly, and probably still is, despite the fancy new name for the hospital, the custom to write for *lotio alba* in strengths designated as "2-ply," "4-ply" and "6-ply." The formula below is for the 2-ply lotion; the 4- and 6-ply were obtained by keeping the total quantity of the lotion constant but doubling and trebling the 2 active ingredients:

Zinc sulfate	ʒij	8.0
Sulfurated potash	ʒij	8.0
Water to make	℥iv	120.0

This is to be applied at night and washed off in the morning with hot water and some such gritty soap as hand sapolio; it has also been recommended that potassium nitrate be added to the water in the proportions of 30 grains (2 Gm.) to the pint (500 cc.). After drying, talcum powder to which has been added 1 drachm (4 Gm.) of sulfur to the ounce (30 cc.), should be freely dusted on. This treatment, because of its violence, has frequently to be interrupted by periods during which only cold cream is used at night and calamine lotion during the day.

Karp *et al.* (1939) reported great improvement in nearly all of the 50 patients whom they treated by the application of a mixture, which forms a slush, of carbon dioxide snow, acetone and sulfur. Dobes and Keil (1940), using this "cryotherapy" method in 115 patients, did not obtain nearly so

good results and reported several unpleasant reactions and a number of contraindications; decidedly it seems to me this treatment should be left to dermatologists to study and not be employed by others as yet.

Certainly a much less violent method than either of the above is that which Swartz and Blank (1944) used in a large number of patients of both the clinic and private practice types. The mixture employed was 25 per cent sulfated oil and 25 per cent mineral oil, and 50 per cent water. A small amount of this mixture is massaged into the face for a few minutes three times daily and then rinsed off with water, the frequency of the cleansing being decreased as the skin becomes less oily—indeed it is a reduction in the oiliness of the skin which is the object of the treatment.

Ultraviolet Light.—This agent is highly capricious in its effectiveness, just as is natural sunlight. It always seemed to me that the only cases deriving more than a superficial specious benefit from its use were those in which considerable peeling of the skin was induced; but its success even in cases burned to this extent was far from predictable in my day. Dermatologists tell me that its status has not changed in the years since I have had any intimate experience with it.

X-Ray.—Pillsbury *et al.* (1942) in the Military Manual of Dermatology stated that superficial x-ray in safe dosage, administered only by specially qualified persons, is the best of all acne treatments—that indeed it accounts for 90 per cent of all good results achieved in severe cases. I imagine, however, that most conservative men will reserve its use for the indurated type of acne which has failed to respond to all other types of therapy and has persisted beyond the "physiological" period.

Other Measures.—I think there can be no better guide for the general practitioner than a résumé of the opinions of the following outstanding dermatologists published in a symposium on acne in the Journal of Investigative Dermatology in mid-1940: Joseph V. Klauder, George M. Mackee, Henry E. Michelson, Hiram E. Miller, Richard L. Sutton, Sr., Udo S. Wile. All agreed that endocrine therapy is without value; vitamins were considered useful only to improve the general health. Five of the six found vaccines and toxoids without value. Anemia was considered to be casually and not causally associated with acne and the administration of hematinics was held of little if any value. Roentgen therapy was regarded as of some but not dominant value in treatment: one of the group resorted to it in about 25 per cent of his cases; one restricted it to patients above fifteen years, another above sixteen, another above seventeen; all were more or less opposed to repetition of a single course; roentgen therapy was felt to be most effective when combined with other measures. Four of the group stressed the importance of extracting comedones and opening pustules; one did not do this and one felt that it might aggravate the condition. The importance of local medical treatment was agreed to by all the group.

WARTS

Warts, as is well known, are seen principally in children, but they may develop for the first time in adults. The most frequently encountered types are: the small, flat, so-called "juvenile" warts, occurring principally on the face and backs of the hands; the larger excrescences, known as verruca vul-

garis, with a predilection for the backs of the hands and wrists but also occurring on all other parts of the body; the plantar wart of the sole; and the projecting, filiform, narrow-based type, seen principally on the face and scalp. It is now believed that warts are caused by a filtrable virus; they seem to be auto-inoculable.

THERAPY

Local Treatment.—Perhaps the most valuable method employed at the present time is fulguration; the lesions turn black and drop off several days after treatment. The use of x-rays is often enthusiastically lauded, and recently radium has been also; doubtless the results are excellent in most cases, but it seems to me that warts are very benign affairs in which to use these potent and dangerous agents; certainly only skilled dermatologic radiologists should be permitted to give such treatments. For the treatment of single lesions in which temporary unsightliness and a certain amount of scarring are not objected to, the use of ethyl chloride, the curet and silver nitrate are quite effective: the site is frozen with the ethyl chloride (which in itself is said to be effective in destroying warts), the lesion is quickly curetted out, and the wound is then thoroughly treated with the silver nitrate stick. Carbon dioxide snow is often effectively used. The following are examples of the great variety of caustics and keratolytics that are applied; they sometimes succeed in accomplishing the removal of the lesions, but the process is usually very tedious.

Salicylic acid.

℞	Salicylic acid	ʒiss	6.0
	Collodion	℥j	30.0

Label: Touch the wart two or three times daily with the solution, having previously removed the adherent collodion.

℞	Salicylic acid	ʒiss	6.0
	Chloral hydrate	ʒiiss	10.0
	Collodion	℥j	30.0

Label: As above.

℞	Salicylic acid	ʒiss	6.0
	Mercurous chloride	gr. xv	1.0
	Hydrous wool fat	ʒv	20.0

Label: Apply to wart several times daily.

Arsenic.—This drug is usually applied in the form of Fowler's solution (U.S.P. solution of potassium arsenite), first softening the lesions by the use of a 5 per cent solution of potassium hydroxide. A modified Marsden paste (Hare) may also be applied if the warts are few:

Arsenic trioxide	gr. lxxv	5.0
Acacia	gr. lxxv	5.0
Cocaine hydrochloride	gr. xxx	2.0
Glycerin	♏xxx	2.0

Water to make a paste.

This is applied on gauze and kept in place for twenty-four to thirty-six hours; the slough is then poulticed away. This is radical treatment.

Strong Acids.—Chromic "acid" is applied in 20 per cent solution. Nitric acid is applied full strength with a glass rod and neutralized with salt solution when it has corroded deeply enough. Both dichloracetic acid and trichloracetic acid (the latter much less expensive) are applied in liquid form with a glass rod.

Vleminckx's Solution.—This, the solution of sulfurated lime of the N.F., was often used by Pusey, who employed a small dressing saturated with the solution to the wart overnight and repeated these nightly dressings until irritation was produced; then the treatment was used less frequently until the wart disappeared or until, in cases of plantar warts, the desiccated horny mass could be dug out.

Urea.—MacKay (1940) found the injection at the base of the wart of 0.1 to 0.2 cc. of 50 per cent urea solution to be useful in about half of a very small series of patients.

Formalin.—Thomson (1943) recorded the successful treatment of 39 cases of plantar warts in three to four weeks by soaking them nightly for ten minutes in 3 per cent formalin solution; the affected part of the sole was placed in the solution in a small saucer so that the thin skin on the top and sides of the foot did not become wetted.

Systemic Treatment.—All of the antisyphilitic drugs—mercury, the arsphenamines, bismuth—have been used much as in the treatment of the major disease. Nitrohydrochloric acid, employed as in hay fever, also has had a trial. Response to any of these drugs is extremely variable, most of the successes apparently being had in cases of warts of the flat "juvenile" type. In 1944, Biberstein reviewed the results he had obtained with the use of a "vaccine" through the years and claimed an effectiveness of about 80 per cent; but since the series of injections extends over a long period of time it seems to me that one may legitimately suspect that other factors are operating to effect these "cures" in addition to the injected material.

Treatment by Suggestion.—In Kentucky, in my childhood, the method was to rub the cut side of a potato on the wart, bury the potato and wait; I do not recall the results. A bit further west, in the land of Tom Sawyer, there was something about a bloody bean and a cat in the graveyard at midnight, if memory serves me correctly. The practice in Timbuctoo is not known to me. In Zurich some years ago, Bloch risked his reputation by asserting his belief that warts could be cured by suggestion; Sulzberger, who studied under Bloch, has stated that he also uses hocus-pocus effectively at times, and others have reported in the same vein. I wonder if this advances us very much?

HERPES ZOSTER

(*Shingles*)

Herpes zoster is an acute inflammatory skin disease characterized by the appearance of crops of vesicles seated upon erythematous bases along the course of one or more of the peripheral sensory nerves, the sites of predilection being the thoracic, lumbar, brachial and supra-orbital regions. In the average case the lesions dry into crusts and disappear in a week or two with little or no accompanying pain, but in severe cases there may be many successive crops of vesicles that persist for a long time and become pustular, rarely even gangrenous; pain of neuralgic character is usually severe in these cases, and in the elderly there is often much pain though the eruption be slight. The disease, which may occur at all ages but is very rare in infancy, is now generally conceded to be a transmissible virus infection of the posterior roots, the ganglia or paraganglionic tissues, with secondary manifestations in the skin. The contention that herpes is an atypical form of chickenpox still remains to be sub-

stantiated. In a few reported cases the inflammatory process has spread from the posterior to the anterior horn cells with production of motor lesions; recovery has usually been very slow in these cases. So few cases of herpes zoster have come to autopsy that the pathology still remains somewhat obscure; reviewing the literature and reporting a case of their own, Krumholz and Luhan (1945) felt uncertain that encephalitis occurred as a complication of the disease. Gais and Abrahamson (1939) stressed the difficulty of differentiating herpes before the eruption from certain intrathoracic and intra-abdominal lesions.

THERAPY

In most cases the only indication is to protect the lesions from traumatism and subsequent infection. For this purpose it usually suffices to apply a dusting powder of thymol iodide and cover the parts with cotton held in place by adhesive strips; or paraffin or collodion dressings may be applied. For the relief of moderate pain the usual analgesics are used. In severe cases the pain is not so easily relieved; resort to the opiates can of course be had, but codeine sometimes does not suffice and the objections to the prolonged use of morphine or dilaudid, or even demerol, are obvious. McDowell (1941) reported prompt and complete relief following the employment of cobra venom in 6 cases, which is unusual since such relief as accompanies the employment of this agent in other painful conditions usually is very tardy in making its appearance. Some years ago Sidlick (1930) reported that most of his 54 patients given intramuscular injections of 0.5 to 1 cc. of pituitrin at twenty-four hour intervals were relieved after only a few such injections; Sulzberger and Wolf (1942) considered this the most effective form of treatment. Baird (1943) well pointed out that pituitrin should be considered contraindicated in the presence of hypertension, coronary disease, myocardial disease and pregnancy, and perhaps in all elderly individuals even in the absence of these conditions. Ruggles (1931) gave intravenously a 20 cc. solution of 30 grains (2 Gm.) of sodium iodide on the first, second, fourth and seventh days in 15 cases, all the patients having been greatly relieved, some not even requiring a full course. Several others have reported favorably upon this iodide treatment, and Sulzberger and Wolf (1942) considered it second in value only to pituitrin, but they warned against iodine intoxication, iodine allergy and iododerma. Secunda *et al.* (1941) infiltrated the areas of hyperesthesia with 0.5 to 2.0 per cent procaine solution with relief of one to thirty hours' duration in 13 of 14 patients. Eight of the patients were subsequently injected with a modification of Hollander's formula (benzocaine 3 per cent, benzyl alcohol 10 per cent, phenol 1 per cent in oil of sweet almonds); there was complete relief of pain in most of these patients but some local and slight systemic reactions were experienced a few times. Rosenak (1938) injected 0.5 per cent procaine solution intravertebrally and paravertebrally, certainly a much more difficult procedure than that of Secunda; however, he reported that pain ceased and the vesicles dried within twenty-four to forty-eight hours in 20 of the 22 patients. Walker and Walker (1938) reported relief from pain in cases involving the eyes and forehead and side of the nose following injection of 5000 units of diphtheria antitoxin; I cannot imagine how one would justify such treatment on rational grounds, but this is true of some of the other types of treatment as well.

Both Sutton and Stelwagon stated that a mild galvanic current (1–5 ma.) is often of very great service in persistent neuralgias. The positive electrode

is placed over the affected ganglion, the negative drawn along the course of the nerve backward toward the cord; it is recommended that the current be used during ten or fifteen minutes each day. Paravertebral alcohol injections are sometimes necessary. It has been said that the occasional spraying of the skin over the affected ganglion with ethyl chloride sometimes effects a reduction in the pain. Smith (1941) injected thiamine solution into and beneath the areas involved in the eruption; his three patients were promptly relieved but I think that one may be justly skeptical of these results until a larger series of cases is reported with proper controls injected with saline only. There have been a number of reports of the successful employment of x-ray therapy over the spinal root ganglia of the nerves involved—for example, McCombs *et al.* (1940) felt that they were successful in checking the pain in 39 of the 44 patients who began treatment within the first seven days of the course of the disease; but I must add that there are many men who are wholly skeptical of the value of roentgen therapy in this malady. Thiamine hydrochloride (vitamin B_1) has been much employed in systemic treatment, large doses being given both by mouth and parenterally since Goodman (1939) reported favorably upon its use in 5 cases; however, Rattner and Roll (1939) were disappointed with it in their 16 cases and so too have been many other men who have not reported their cases in the literature—indeed, Steinberg (1938) described 3 cases of typical herpes zoster occurring apparently as a complication of the administration of large amounts of thiamine.

PRURITUS ANI

There are many ascertainable causes for itching about the anal region, such as constipation, colitis, cirrhosis, carcinoma, anal fissure, hemorrhoids, pinworm infestation, bacterial or mycotic infections, diabetes mellitus, etc. Removal of the cause will bring complete relief in many instances, but there also exists a class of cases to which the word "idiopathic" can be correctly applied since they are associated with no demonstrable etiologic factors and respond but poorly to the milder types of treatment. Very interestingly, however, Foster and Hill (1940) have drawn attention to the frequency with which attacks of pruritus ani occur in association with exacerbations of seborrheic dermatitis of the scalp, ear canals, eyelids, umbilicus, or axillas, or of dermatophytosis of the feet.

Local Antipruritic Measures.—Absolute cleanliness is essential, the parts being washed after every defecation. Oftentimes the application of a hot wet pack for a few minutes after washing brings relief which persists for a half hour or more. The following are examples of the antipruritic ointments that are most frequently used:

Yellow mercuric oxide	gr. xx	1.2
Hydrous wool fat	℥ij	60.0
Petrolatum to make	℥iv	120.0
Ammoniated mercury	gr. xl	2.4
Hydrous wool fat	℥ij	60.0
Petrolatum to make	℥iv	120.0
Crude coal tar	ʒiij	12.0
Zinc oxide	ʒiij	12.0
Petrolatum to make	℥iv	120.0

The amount of coal tar contained here, 10 per cent, may be much increased.

Phenol	gr. xl	2.4
Zinc oxide	ʒiij	12.0
Ointment of rose water (U.S.P.) to make	℥iv	120.0

Phenol	♏xx–xl	1.2–2.4
Menthol	gr. xx–xl	1.2–2.4
Ammoniated mercury ointment (U.S.P.)	℥j	30.0
Zinc oxide	℥j	30.0
Anhydrous wool fat	℥ij	60.0
Lime water to saturate and make ointment.		

Ethyl aminobenzoate (benzocaine)	ʒiij	12.0
Salicylic acid	gr. xlv	3.0
Hydrous wool fat to make	℥iv	120.0

Benzyl alcohol	ʒiss	6.0
Hydrous wool fat to make	℥ij	60.0

Injection Therapy.—Since 1916, when Stone introduced perianal injection methods, many solutions have been used with varying success: alcohol, dilute hydrochloric acid, phenol, etc. Gabriel's formula, introduced by him in 1930, has won many advocates, since it contains an anesthetic, nupercaine, phenol, which apparently intensifies the anesthetic action, and alcohol, which destroys the nerve filaments. The proportionate constituents are nupercaine, 0.5 per cent, benzyl alcohol, 10 per cent, and phenol, 1 per cent in sterilized sweet almond oil. With this mixture it is said that anesthesia generally persists for two to six weeks, there is no pain in the injection itself except the first prick of the needle, there is very little likelihood of sloughing occurring, no systemic reactions, and a procedure simple enough that it can be employed in the office. In 1936, Steinberg reported that in a series of 100 patients followed over a period of two years or longer, the results were excellent in 51 per cent, and satisfactory in 73 per cent; in all instances temporary relief of at least one month was obtained. Steinberg's technic follows:

"The perianal skin is cleansed with tincture of green soap and painted with Scott's solution (mercurochrome crystals 2 parts, distilled water 35 parts, acetone 10 parts and alcohol 55 parts) or tincture of merthiolate (1:1000). One ampule of nupercaine-phenol-benzyl alcohol in oil, which has been slightly warmed to facilitate the flow of oil, is drawn into a 5 cc. sterile glass syringe through a large caliber needle. The needle is then changed to one of gauge No. 21, $1\frac{3}{4}$ to 2 inches long. The perianal region is then divided into four quadrants, and usually either the left or right posterior quadrant is chosen first. The patient should lie in the Sims' position, on the side selected for the treatment. The needle is inserted subcutaneously about one-half inch outside the affected area. *It must be freely movable at all times.* The solution is then injected in fan-shape manner until all the 5 cc. have been used. *The injected tissues are massaged gently for about 3 minutes* with a sterile piece of gauze, thus assuring an even distribution of the oily solution. The second injection is given 2 days later in the opposite posterior quadrant, and, at 2-day intervals, the two anterior quadrants are treated in a like manner. *Great care should be taken not to inject the solution too superficially or intradermally, as sloughing will invariably follow.* The external sphincter muscle should not be injected, because if more than one quadrant of the muscle has been injected, the anal canal may become patulous and temporary loss of control take place."

Tattooing.—Just about the latest of the thousand and one treatments advocated for control of pruritus ani is the tattooing of the region with mercury sulfide. Turell (1940), and Cantor (1943), reported good results in cases refractory to other more usual types of treatment, but it would seem that this is a specialist's type of therapy.

Surgery.—Surgeons are performing perianal subcutaneous neurotomy which they say is effective in stopping the itching; Cantor (1943) in some instances combined the tattoo and neurotomy approaches.

X-Ray.—This agent, in the hands of a properly qualified expert, will by no means relieve every case but it does have some brilliant successes to its credit. Upon the other hand, the relief it affords is seldom permanent and many men feel that the pruritus which returns after a period in which it had been held in temporary abeyance as a result of the treatments is far worse than that originally treated.

SCABIES

Scabies is an infectious disease caused by an animal parasite, *Sarcoptes scabiei*, the female of which incites the itching by burrowing into the skin in order to lay her eggs. These burrows, which are tortuous and marked by a slight elevation at one end and a grayish speck at the other, can be seen with a strong hand lens. The sites of predilection are the dorsal surfaces of the webs between the fingers, the anterior axillary fold, the lower abdomen, the nipple region in the female and the shaft of the penis in the male. In cleanly individuals the spread is usually not beyond these points, but in dirty individuals and in severe cases the whole body may be involved, though the face and scalp nearly always escape. In children the palms and soles are also often infested; superimposed eczematous and impetiginous lesions are also frequent in young patients and in patients of any age who do not resist the desire to scratch excessively. The disease probably never disappears spontaneously. In England during War II scabies became a veritable scourge due to crowding in the shelters, the wide scattering of evacuees throughout the country, and probably the jamming of the "tight little island" with its own and our soldiers. Experience in this epidemic amply proved that all contacts of the infected patient must be treated if cure is to be effected. Graham's (1944) figures showed that irrespective of the size of the family, if scabies gains an entrance to the household 80 per cent of the members are infected. As long ago as 1687, Bonomo showed that scabies is associated with the presence of *S. scabiei;* indeed this was the first infectious disease to have its etiology established.

THERAPY

Benzyl Benzoate.—Kissmeyer popularized the use of this agent in 1937, and the British epidemic during War II fully established its superiority to sulfur; the study of Mellanby *et al.* (1942), in which benzyl benzoate was compared with many other agents, was the most exhaustive. The impression of many observers, confirmed by the studies of Lunn (1942), is that benzyl benzoate is just as effective whether a bath is given beforehand or not, though in very severe infections in which there is incrustation it is still considered advisable to give a good scrubbing bath before applying treatment. Experience has also

shown that one thorough treatment is all that is needed; the definitive experiment in this connection was that of Mellanby (1944), who reported an incidence of 26 per cent of scabies among the female patients in a large institution for the insane—after a single treatment of all 804 patients (without preliminary baths), and of such members of the staff as were infected, all evidence of the disease disappeared and there was only a negligible number of recurrences.

Kissmeyer's original formula consisted of equal parts of soft soap, isopropyl alcohol and benzyl benzoate, but accumulating experience has shown that the smarting sometimes caused by the alcohol in this lotion is disagreeable and indeed may even stalemate the effort to rid a district of scabies through effecting reduction in attendance at clinics. In England the most popular substitute for the Kissmeyer lotion was an emulsion or "cream" with the following formula:

	Gm. or cc.
Benzyl benzoate	200
Lanette wax S X	10
Water	800

Directions: Add the benzyl benzoate to the wax heated on a water-bath and pour the water into the mixture when both are at a temperature between 60° and 70° C.; stir until cold.

This cream is to be thoroughly rubbed over the body from the ear-chin line down, giving especial attention to the sites of predilection for the burrowing of the mites. The patient puts on the same clothing again and after twenty-four hours takes a thorough soap bath and changes to fresh clothing and bed linen. While not doubting that clothing and bedding may play some part in the spread of scabies, British observers during the epidemic came to the conclusion that this part was very minor and that therefore disinfestation of fomites was not a matter of great importance; indeed the Ministry of Health issued an amended routine procedure, emphasis being laid rather on the follow-up and treatment of the family and other close contacts of the original case.

Slepyan (1944) described the effective use in the U. S. Navy of the following formula:

	Gm. or cc.
Benzyl benzoate	250
Duponol C (E. I. du Pont de Nemours)	20
Aqueous bentonite solution (2.5 per cent) to make	1000

Directions: Pour the benzyl benzoate gently over the duponol C and then add the bentonite solution slowly without shaking; finally agitate the emulsion until all the duponol C is dissolved.

Slepyan's method of employing this preparation was more ritualistic than that of the British: the patient was first scrubbed in a soap bath, two applications of the lotion were then made with a five-minute interval for drying in between, the patient was then put to bed well covered with blankets and kept there for four hours, the lotion was then showered off, and clean clothes were supplied.

Dermatitis is an extremely rare occurrence with the benzyl benzoate treatment.

Sulfur.—*The older method* of using sulfur to combat scabies was advocated by Pillsbury *et al.* (1942) in the Military Manual of Dermatology. After a vigorous soap and scrub bath, sulfur ointment of 10 to 15 per cent strength (U.S.P. XII sulfur ointment is 15 per cent) is rubbed in vigorously with special attention to the regions of predilection, a thick coating of ointment being left

on and the patient put to bed wearing clean pyjamas. This treatment is repeated vigorously each morning and evening for three consecutive days without bathing or change of bed linen during that time. On the third evening the patient takes a hot scrub and soap bath, applies a soothing lotion if necessary after drying the body, and retires in clean pyjamas in a clean bed. This will do of course for military personnel under rigid control, but in ordinary civilian practice it is usual for the ointment to be applied only at night extending the period for five nights in some instances. This "standard" sulfur treatment is quite likely to cause some degree of itching dermatitis even if the ointment is applied only once daily.

The "Danish" method of using sulfur is thought by many to be superior, but the opinion is not unanimous; quicker it certainly is, but some men claim it is less effective than the slower method and more likely to be followed by dermatitis. The patient merely applies the ointment—which is a rather complex one and is now available commercially as Tilden's Danish scabies ointment and also as Scabicide of the Upjohn Company—after a preliminary bath and drying, goes to bed for twenty-four hours, and then removes the ointment, with bath and clean linens as in the older method.

The *lather tablet method*, introduced by Carter (1941), in England, employs a tablet containing sulfur incorporated with a lathering agent, the advantage being that the overzealous cannot apply too much sulfur when employing it in this form. Three successive treatments are given: (*a*) hot scrub bath; (*b*) rub up the tablet between the wet hands and apply the lather all over the body; (*c*) put on the underwear after the lather has been allowed to dry on the body. Mellanby *et al.* (1942) did not find this method of treatment very effective.

Sodium Thiosulfate and Acid.—This method is designed to release nascent sulfur on the surface of the body. The patient paints the whole body below the ear-chin line with a 40 per cent solution of sodium thiosulfate, allows it to dry for fifteen minutes, then paints a 5 per cent solution of hydrochloric acid over the thiosulfate and allows it to dry for fifteen minutes, then repeats the entire treatment after two hours. Fresh linen is then given and the whole procedure repeated on the next day, a bath being taken twelve hours after the second day's treatment. If further treatments are required an interval of three to five days is allowed to elapse; in children under seven years the strength of the solutions is cut in half. Mellanby (1942), in his comparative study of all sarcopticidal agents, found this method troublesome to use and the results so unsatisfactory that he could see no reason for continuing with it; furthermore he found that it lends itself to zealous overtreatment.

Sulfur Internally.—Berncastle (1941) reported that he had used sulfur effectively internally during War I, but Mellanby *et al.* (1942) found that even if sulfur is taken in as large a dose as can be consumed without causing severe physical discomfort parasites appear to be entirely unharmed; so this bubble is apparently exploded.

Rotenone and Derris Root.—Derris root and its active principle, rotenone, have been given a thorough trial since they are effective in the destruction of insects which infest animals. However, experience has shown these preparations to give rise very frequently to severe dermatitis, and Mellanby *et al.* (1942) in their comparative studies found the preparations much less effective than sulfur ointment.

Tetmosol.—The newest agent to be tried in the treatment of scabies is

tetraethylthiuram monosulfide, conveniently shortened to "tetmosol." So far as I am aware the studies have been confined to England and have been of a rather experimental nature. Percival (1942) found a 5 per cent solution curative in 50 consecutive hospitalized or ambulatory patients. Clayton (1943) used it in greater strength, employing a formula containing tetmosol 25 per cent, polyglycerol ricinoleate 10 per cent, alcohol 65 per cent. Clayton made three or four applications of this mixture at three- to four-day intervals and was very pleased with his results in a small series of cases; dermatitis was not induced. Bradshaw (1944) found a lotion containing 6.25 per cent of tetmosol reliably effected cure in three days in 97 per cent of 67 cases; the patient was given a hot scrub bath, dried and the lotion applied and then the clothing put on after allowing time for the lotion to dry, the seance being repeated on three successive days. Bartley *et al.* (1945) substituted 5 per cent tetmosol soap for ordinary soap in a closed community of 400 persons with the following results: during eighteen weeks when an ordinary soap was used, 21 new cases of scabies occurred; during the thirteen weeks after the substitution of the tetmosol soap only 1 new case occurred and that during the first six weeks; no instances of dermatitis were recorded.

SCHISTOSOME DERMATITIS

(*Swimmer's Itch*)

(See chapter on Flukes)

BODY LOUSE INFESTATION

During War I soldiers were deloused through bathing, shaving and the application of insecticidal agents; clothing and bedding were treated by steam sterilization; and it was all a very cumbersome and time-consuming business. During War II clothing was deloused through methyl bromide fumigation, a method so simple that it was said a fumigation and bath company of 88 men could delouse the clothes of an entire division in forty-eight hours. There were also developed in all of the armies new insecticidal agents for delousing the soldier himself. The first standard louse powder adopted by our own army was known as MYL, a mixture of pyrethrum and an activating substance which increased its effectiveness about 40 times. This powder had been used experimentally in native villages in Mexico and Egypt and had been found very effective, but in 1942 a change in the monsoon season in Kenya, East Africa, the source of supply of pyrethrum, resulted in a drastic reduction in the production of this agent and therefore in our supply of MYL powder. As a result, the U. S. Department of Agriculture, which had been responsible for the production of MYL, directed attention to the chemical dichlor-diphenyl-trichlorethane, the formula for which had been released to both the British and ourselves by the Swiss firm that held the patent. Extensive studies soon showed the high degree of effectiveness of this agent against lice and other

insects, and in May, 1943, the Army adopted as its standard powder one containing 10 per cent of this chemical, now known popularly as DDT. Experience has shown the superiority of DDT to any insecticide hitherto known. If an individual's clothes are thoroughly dusted with DDT powder, Simmons (1944) said he will remain free of lice for as long as a month even though the clothes are washed at weekly intervals. Furthermore, the blowing of the powder down the neck or up the sleeves of an individual will delouse him without the necessity of his removing his clothing or bathing. It was this last method of employment which brought to a sharp close the epidemic of typhus in Naples during the time of our conquering campaigns in Italy in 1943. In December of that year about 50 cases of typhus were being reported daily in a population which was highly susceptible to this disease through having been free of it for generations, and there was certainly every reason to believe that a devastating epidemic was imminent; however, by March of 1944 more than a million and a quarter persons had been treated at delousing stations (in one day 73,000 were "powdered"), the epidemic in Naples was brought to a close, and the disease did not spread at all to American troops in Italy. How the late Hans Zinsser would have relished that triumph over the louse!

But at the time I write DDT is not yet released for civilian employment and therefore in nonmilitary practice, where isolated instances of louse infestation are occasionally seen, we must still resort to the older measures. It often suffices in cases of light infestation to have the patient take a good cleansing bath with soap and hot water and later apply one of the mercuric chloride lotions used in the treatment of crab louse infestation, preferably the one without alcohol which would likely be disagreeable for a few moments if there is severe excoriation. In some instances it may later be necessary to use one of the soothing lotions or creams if scratching has excessively irritated the skin. The clothing and bedclothing must then be disinfected by autoclaving in 130° F. (50° C.) for thirty minutes, or 140° F. (60° C.) for fifteen minutes, or by employing methyl bromide fumigation as is done in the Army: the clothing of the individual is placed in a gas-proof bag and a small ampule of methyl bromide is broken into the bag. Ironing the clothing and bedding with hot irons is at best only a makeshift method by no means reliable. Disinfecting fluids in which clothes may be placed for twenty to thirty minutes: (*a*) gasoline; (*b*) cleaner's naphtha; (*c*) compound cresol solution at a temperature above 32° F. (0° C.).

HEAD LOUSE INFESTATION

Kerosene.—The ordinary grocer's kerosene is usually diluted with equal parts of olive or cottonseed oil to render it less inflammable; the scalp is then thoroughly soaked with this mixture and covered with a loose cloth. The head should be kept covered for twenty-four hours, after which the mixture is to be thoroughly washed out with soap and warm water. The treatment may be repeated as often as is necessary with intermissions of a few days.

This treatment is fairly effective in killing the lice, but it does not destroy most of the nits at the first application. The fine comb should be freely used between treatments.

Xylol.—The usual mixture used is equal parts of xylol, alcohol and ether; this is of course very inflammable but evaporates quickly. One thorough treatment of the scalp and hair with this preparation usually suffices to kill all the lice and nits, but the latter adhere more tightly to the hairs after being killed in this way than they do while alive. The fine comb must be diligently employed; it has been said that vinegar will wash out the nits, but Buxton (1940) stated that this positively is not so. The treatment can, of course, be repeated if necessary.

Mercuric Chloride.—The bichloride of mercury is used 1:500 in 50 per cent alcohol as follows:

℞	Mercuric chloride (bichloride)	gr. xv	1.0
	Alcohol	Oss	250.0
	Water to make	Oj	500.0
	Label: Apply to hair and scalp as directed.		

The hair and scalp are thoroughly anointed with this solution twice daily for three or four days. This is a very clean method but if the scalp is abraded the alcohol is likely to cause considerable momentary smarting pain.

Larkspur.—This substance is not so much employed nowadays as formerly, any of the three previously listed mixtures being superior to it in most instances. It is perhaps best employed in the form of the acetic tincture of larkspur (N.F. VII). Larkspur is poisonous and if there are abrasions of the skin may be sufficiently absorbed to cause symptoms like those of excessive aconite action: tingling of mouth and skin, gastro-intestinal symptoms, restlessness, collapse.

Lethane.—In 1942, Busvine and Buxton in England drew attention to several new insecticides for use against head lice, of which lethane-384-special has subsequently had the greatest trial; this compound, obtainable from Rohm and Haas in Philadelphia, contains 12.5 per cent N-butyl carbitolthiocyanate, 37.5 per cent beta-thiocyanothyl laurate, and 50 per cent liquid petrolatum. The preparation is applied by rubbing several teaspoonfuls of it well into the scalp with the fingers and then avoiding too much combing thereafter, which is said to draw the insecticide away from the scalp; patients are told not to wash their head for ten days. There seems to be no doubt that lethane is very effective in killing lice; Busvine (1943) said that the nits are killed also, but Gamlin (1943) did not believe this to be true. In any case, Gamlin found that if the hair is first saturated with a 2 per cent solution of Lysol at a temperature of about 104° F., then combed for the removal of lice and nits, and then the lethane applied the method is 100 per cent successful in the destruction of both lice and nits. According to Scobbie (1945), lethane has an unpleasant and persistent smell and gives the hair a greasy appearance; it does not seem to be irritant or toxic.

D.D.T.—Scobbie (1945), employing a D.D.T. emulsion not yet commercially available, found it the best of all the agents which she tested both experimentally and clinically; all the lice are killed and the D.D.T. remains in the hair long enough to kill all the larvae as they hatch. It is said that the D.D.T. emulsion does not have an unpleasant odor and that the hair does not look greasy and unnatural after its application; it seems to be neither toxic nor irritating.

Benzyl Benzoate.—Blackstock (1944), in England, said that if benzyl benzoate is applied in the form of an emulsion known as ascabiol (new formula),

a May and Baker product, not only are the lice and nits killed but the latter may be simply removed by washing the hair with soap and water twenty-four hours after the application is made. However, Scobbie (1945) found that ascabiol killed only 80 to 90 per cent of the nits and that in her experience they were not removed as simply as had been claimed by Blackstock.

Phenyl Cellusolve.—This agent was used by Davis *et al.* (1944) very effectively in a small study at Bellevue and a large field study in Mexico, the formula employed being:

Phenyl cellusolve (Carbon and Carbide Chemicals Corp.)	40 per cent
Ethyl alcohol	30 per cent
Methyl salicylate (to give odor)	5 per cent
Water	25 per cent

Both lice and nits were declared to have been killed but the nits were left on the hair. Subsequently, Hansens (1945) in New York tried out lotions containing 5 per cent, 10 per cent and 20 per cent respectively of phenyl cellusolve and found them all effective in destroying both living lice and nits as shown by examinations made one day, one week and three weeks after treatment; he used enough of the lotions to wet the hair thoroughly, taking care that the lotion did not run into the eyes and applying it particularly well behind the ears and in other areas where nits and lice might be concentrated, and then giving the hair a shampoo four hours later. Skin irritation resulting from the phenyl cellusolve treatment has not been reported to my knowledge.

CRAB LOUSE INFESTATION

At the time of writing it is not known to me whether the Army insecticidal powder developed during War II (see Body Louse Infestation) is effective against crab lice, though presumably it is; the following therefore is merely a list of the chief agents in use in civilian practice pending release of the Army powder for commercial distribution. One should interpolate, however, that O'Donnell (1944) has reported the satisfactory use of the Freon bomb, playing the spray over the entire body for about ten seconds from a distance of 12 to 16 inches, the patient being enclosed in a small tent; crab lice were reported absent after twenty-four hours and in four days the nits had disappeared; patients were advised not to bathe for at least twelve hours after spraying to avoid cutaneous irritation.

Any of the following preparations will usually be effective if applied several times daily, but their use must be accompanied by the frequent and vigorous employment of soap and water, and in severe cases the pubic region must be shaved and the hair on the abdomen, thighs, lower part of the back, chest, axillae, eyebrows and border of the scalp must be thoroughly searched for nits.

Mercuric chloride	gr. iv	0.25
Alcohol	℥iv	120.0
Water to make	℥viij	240.0

(The bichloride in this and in the following formula is present in the approximate strength of 1:1000; occasionally this will cause a mild dermatitis, in which case its use should of course be stopped.)

Meruric chloride	gr. iv	0.25
Diluted acetic acid	ʒiij	12.0
Water to make	℥viij	240.0
Tincture of cocculus (N.F. V)	℥ij	60.0
Alcohol	℥ij	60.0
Water to make	℥vj	180.0
Ammoniated mercury	ʒiss	6.0
Hydrous wool fat	℥j	30.0
Petrolatum to make	℥ij	60.0
Ointment of yellow mercuric oxide (U.S.P.)	℥ij	60.0
Strong mercurial ointment (U.S.P.)	℥ij	60.0
Xylol	℥ss	15.0
Hydrous wool fat	℥j	30.0
Petrolatum to make	℥ij	60.0

ACUTE POISONING

THE CORROSIVE ACIDS AND ALKALIS

The corrosive acids and alkalis most frequently swallowed accidentally or with suicidal intent are sulfuric, nitric, hydrochloric and oxalic acids, sodium or potassium hydroxide (lye), sodium or potassium carbonate, and ammonium hydroxide (household ammonia). The general symptoms of the group are: corrosion of the mucous membranes from the lips down to the pylorus; extreme pain, soon followed by the vomiting of food, shreds of mucosa, mucus, and blood that is dark brown due to the conversion of hemoglobin into hematin and other products; profuse bowel movements that are at first normal but later contain blood and shreds of mucosa; respiratory symptoms due to contact of some of the corrosive material with the air passages; and quick shock and collapse. Those escaping immediate death may succumb to perforation of the stomach or the symptoms resultant upon stricture of the esophagus or pylorus. In addition, the takers of concentrated ammonia are subject to early unconsciousness and standstill of the heart, and those having swallowed oxalic acid (much used as a bleaching agent in the household) develop calcium deprivation symptoms, such as cramps, headache, convulsions, etc.

THERAPY

Acids.—The acid must be quickly diluted with large amounts of water and neutralized with alkalis. Sodium bicarbonate, sodium carbonate, milk of magnesia, chalk, soapsuds, plaster from the wall, or any other alkali at hand will serve; it should be given in relatively weak concentration but in large quantity. Later, milk, egg white, starch mucilage, acacia emulsion, or any bland oily substance such as liquid petrolatum or butter will be soothing. Supportive drugs as indicated. The value of morphine or dilaudid in decreasing pain and thus perhaps avoiding shock should not be overlooked. Keep the patient warm.

Oxalic acid requires certain special mention, for the reason that the alkalis form salts with it that are more soluble and more toxic than the acid itself, and therefore they cannot be used. Calcium and magnesium salts, however, unite with the acid to form insoluble salts, wall plaster is acceptable, even though it is alkaline, and so too is lime water. It should be noted that patients may experience the calcium deprivation symptoms even though they have taken too small a dose of the oxalic acid to cause the corrosive symptoms; in such cases 1/10 grain (0.006 Gm.) of apomorphine hydrochloride, administered hypodermically, is indicated as an emetic. Action must be quick in the treatment of these cases for the poison is rapidly absorbed. The intravenous administration of calcium is of course also indicated (see Lead Poisoning).

Lye and Other Alkalis.—The treatment is the same as for poisoning with corrosive acids, save that here weak acids are used as antidotes, usually in the form of lemon juice or vinegar, diluted several times with water. Crowe (1944) stated that patients with early poisoning due to lye can be saved the ordeal, expense and dangers of secondary stenosis of the esophagus by the use of Bokay prophylactic esophageal dilation; this is of course work for a specialist.

PHENOL (CARBOLIC ACID) AND LYSOL POISONING

The symptoms are those of corrosive poisoning with additional early evidences of severe nephritis. The toxic action on the cardiovascular and central nervous systems is pronounced and almost immediately manifested; death sometimes occurs in a few minutes, often within the hour.

THERAPY

Lavage, supportive treatment, morphine or dilaudid, and the later use of demulcents, as in all corrosive poisoning, is the obviously indicated therapy. As to antidotes for phenol it seems that sodium sulfate is still the most valuable; it should be used by lavage, 4 drachms (15 Gm.) to the pint (500 cc.) of water, the washing to be continued until the phenol odor disappears. Baumann and Preusse suggested this measure many years ago because of the known conjugation of phenol with sulfuric acid arising in metabolism, the products being eliminated as comparatively harmless ethereal sulfates or sulfonates. Latterly, however, the chemistry of this reaction has come to be doubted, but the measure is a very valuable one nevertheless, perhaps due to some hindrance it offers to absorption plus the induced purgation.

Alcohol has been shown by clinical and experimental observation to be of no value. The same is true of glycerin. Indeed, alcohol if given as an antidote after the poison has been taken may hasten death, despite the well-known fact that a drunken individual swallowing phenol is not so seriously affected as is a normal person. These apparently contradictory facts are not understood. Gibbs (1931) recommended the administration of as large quantity of liquid petrolatum as the patient can be induced to swallow, the endeavor being to have the phenol taken up by (*i.e.*, dissolved in) this nonabsorbable oil; but Bowdler, a former phenol manufacturer, questioned the soundness of the procedure on the basis of his experience that phenol is not readily soluble in liquid petrolatum in the presence of water. Gibbs' reply was not very convincing; Goodman and Geiger (1935) failed to substantiate his contention experimentally, but they did find olive oil to have some value in rats. Travell (1939) recommended that olive, cottonseed, codliver or castor oil be administered in large quantity as a first aid measure, but I have seen no case reports of the employment of such procedure.

MERCURIC CHLORIDE (BICHLORIDE) POISONING

By the time the patient is seen he has usually vomited so profusely that he is now merely retching unproductively or at most is bringing up pink mucoid material; often he is passing reddish watery stools. Abdominal pain is usually very severe unless the patient is already in shock.

THERAPY

The treatment of mercuric chloride poisoning is very unsatisfactory for the reason that practically all patients who have taken as many as 3 of the large U.S.P. tablets or 12 of the small tablets, containing approximately $7\frac{1}{2}$ grains (0.5 Gm.) and 2 grains (0.12 Gm.) respectively, regularly develop anuria on

about the fourth day, and almost as regularly die from lesions of the kidneys, liver, or colon. I do not mean that none are ever saved, because of course they are, but the number saved is pitifully small compared with the number that die.

I shall outline briefly below the two types of therapy chiefly employed nowadays, later appending a word on "specific" antidotes and surgical measures. Morphine or dilaudid is of course indicated in any case.

Treatment Designed to Accelerate Excretion of Mercury.—Since the introduction of this routine by Lambert and Patterson, in 1915, it has probably been used more often than any other, at least here in the United States.

(*a*) On admission, the stomach is lavaged with water, the washings being examined for mercury (which may not appear in the urine for three to twenty-four hours), and a pint of milk is introduced. Parenthetically, one may note that Sollmann *et al.* (1927) found raw eggs and milk equally valuable in precipitating bichloride, but that milk will act more promptly by reason of spreading more rapidly over the stomach; egg white has no advantage over whole eggs. Lavage is repeated at hourly intervals until nausea and vomiting are allayed so that step (*b*) can be taken.

(*b*) Give every other hour by mouth 8 ounces (250 cc.) of the following mixture: potassium bitartrate, 1 drachm (4 Gm.); sugar, 1 drachm (4 Gm.); lactose, ½ ounce (15 Gm.); lemon juice, 1 ounce (30 cc.); boiled water, 16 ounces (500 cc.). Administer 8 ounces (250 cc.) of milk every alternate hour.

(*c*) Employ continuously drop rectal administration of a solution of potassium acetate, 1 drachm to the pint, to promote the secretion of urine; do not stop this enteroclysis day or night except during the irrigations.

(*d*) Wash out the stomach twice daily, and irrigate the colon twice daily to wash out the excreted mercury.

(*e*) Give the patient a daily sweat in a hot pack.

(*f*) Two examinations of the urine for mercury, found negative on successive days, indicate that the treatment may be stopped.

Treatment Designed to Combat Shock, Dehydration and Salt Depletion.—This method of treatment, introduced by Peters, Eisenman and Kydd (1933), has been quite successfully employed with more or less slight modifications by a number of observers since.

(*a*) Emergency treatment by gastric lavage and milk or eggs as in the older treatment above outlined, but subsequent lavaging is not routinely performed nor is the patient given fluids by mouth in the beginning.

(*b*) Give 1 large intravenous infusion of saline as soon as possible, and blood transfusion if evidences of shock are present or appear. If in the latter case transfusion cannot be effected at once, substitute the simultaneous intravenous injection of 10 per cent dextrose solution and the subcutaneous injection of physiologic saline solution.

(*c*) Give saline and dextrose injections, and blood transfusions, in quantities and intervals so regulated "as to insure the presence in the body of a large, but not excessive, supply of fluid of nearly normal composition and to maintain circulatory efficiency." Hull and Monte (1935) set the amount of fluid for the first forty-eight hours arbitrarily at 4000 to 6000 cc.; later this is reduced to 3000 cc., and if edema appears, to 1800 cc. (omitting salt) merely to balance the daily fluid loss via the skin and lungs.

(*d*) If there is no diarrhea, rectal treatment is not given; if there is, a single small cleansing enema is administered daily.

Specific Antidotes.—A number of men are earnestly engaged in this search, but so far the truly specific agent has not been found. The two following are the ones at present outstanding.

Sodium Thiosulfate.—This drug has been used very widely on the theory that it effects the conversion of the poison into the harmless mercuric sulfide. The results are conflicting—*i.e.*, they are of such nature that some physicians loudly praise the drug and others loudly condemn it as worthless. The usual procedure is to administer intravenously 15 grains (1 Gm.) in 10 cc. aqueous solution, once or twice daily. However, in a very severe case, Marchbanks *et al.* gave 10 cc. every eight hours until the patient had 5 doses, and Blaisdell stated that in his hospital 10 patients had been treated without a death after it became the routine practice to give 90 grains (6 Gm.) daily for three to five days. It is strange that it has not been found possible (see Melville and Bruger) to show a prolongation of life in laboratory dogs by this method.

Sodium Formaldehyde Sulfoxylate.—Rosenthal introduced this drug after satisfactory animal experimentation, partially confirmed by Brown and Kolmer (1934). The drug acts by reducing the mercuric chloride to mercurous compounds; no harmful effects of the therapy have been observed. Rosenthal's technic: (*a*) Gastric lavage with 5 per cent solution of sulfoxylate, leaving 200 cc. in the stomach. (*b*) Immediately thereafter, intravenous administration during twenty to thirty minutes of 10 Gm. in 100 to 200 cc. of water. (*c*) In severe cases, repetition of the intravenous injection six hours after completion of the first, but the dose to be only 0.1 Gm. per kilogram (2.2 pounds) body weight and a total of 5 Gm. not to be exceeded for the adult of average weight. There have been a few favorable reports from the use of this method of treatment but some adverse ones as well; for example Monte and Hull (1934) saw no indication of alleged antidotal value in the 7 cases in which they used sodium formaldehyde sulfoxylate. Wolpaw and Alpers (1942) slightly modified the technic in the treatment of their 20 patients in that colonic irrigations of 4 to 5 liters of 0.1 per cent sodium formaldehyde sulfoxylate were given twice daily in addition to the initial gastric lavage and intravenous injections as employed by Rosenthal and gastric lavages with the agent were also employed twice daily; 16 of their 20 patients recovered.

Surgical Measures.—*Cecostomy.*—A number of pathologists have been impressed by the gangrenous colitis observable oftentimes at autopsy, to which Berger *et al.* (1932) gave some sort of expression by advocating immediate cecostomy as soon as the patient is admitted and then the institution of constant colonic lavage. The discussion of their paper by Krumbhaar and others indicated considerable reticence in accepting proof of the necessity for this radical step in all cases; however, Abeshouse (1945), in an extensive review of the subject, felt that best results follow the combined employment of gastric lavage, cecostomy and the intravenous administration of fluids.

Decapsulation.—This is the older surgical approach in anuric cases. Certainly the enthusiasm for it is hardly effusive even among the surgeons; however, Herman (1936), Pennsylvania Hospital, said "Our small personal experience does not justify advocacy of decapsulation and yet I feel, in view of the poor results obtained by other methods, that this procedure should not be discarded without further trial." He made the point that it adds little or nothing to the patient's burden and should probably be employed early in the anuric state. In the case of Reif and Bramley (1943) the function of the decapsulated was much better than that of the nondecapsulated kidney as

evidenced by differential urinary output, indigo carmine tests and intravenous urography. Nevertheless, Abeshouse (1945) felt that decapsulation is contraindicated unless oliguria and anuria have developed in spite of a trial of cecostomy.

GASOLINE, KEROSENE AND TURPENTINE POISONING

The most comprehensive report of gasoline and kerosene poisoning to date is that of Nunn and Martin (1934), who summarized the findings in 72 cases in children. Total mortality was 11 per cent, the children who finally succumbed having lived from two to eighteen hours after ingestion and aspiration of the substances. Apparently ingestion alone need not cause great anxiety; the patients manifested restlessness, incoordination, cyanosis, vomiting and loose stools, but there were no signs of pulmonary involvement, and after a succeeding period of depression, which lasted only a few hours, the children were apparently out of danger. They responded well to emptying of the stomach, stimulation and catharsis (Machle, 1941, stressed the importance of lavage even though forty-eight hours or more have elapsed before treatment is begun, and Deichmann *et al.*, 1944, thought it highly important to continue it until the odor of kerosene is no longer detected in the washings, but Lesser *et al.*, 1943, felt that, since lavage may provoke aspiration, it is probably inadvisable to employ it unless the amount of kerosene ingested is very large). But in the patients who aspirated as well as ingested one of these petroleum products the picture was much graver owing to the rapid development of pneumonitis, as evidenced by cough and many moist râles throughout both lungs. These patients developed rapid and weak respiration and pulse, became cyanosed and restless, and developed coma and convulsions, and often died. In the 33 patients of Lesser *et al.* (1943), pulmonary manifestations were observed in 77 per cent of those examined roentgenologically as compared with only 24.2 per cent found by physical findings alone. Waring (1933) found no evidences of methemoglobin formation in the blood. No really effective treatment has been developed for these serious cases. Nunn and Martin felt that oxygen-carbon dioxide therapy was helpful in their later cases; however, Deichmann *et al.* (1944) pointed out that kerosene remains in the lungs because of its low volatility and that increased pulmonary ventilation would likely have no beneficial effect other than to prevent anoxia or to eliminate it if already present. These last observers also felt that kerosene reaches the lungs not only by aspiration but by way of the blood stream after absorption in the gastro-intestinal tract; and they felt it permissible to employ sulfonamides in the attempt to prevent pneumonia and desirable, where conditions permit, to protect the liver with a diet containing generous amounts of carbohydrate and protein and little fat together with liberal use of vitamin supplements.

Turpentine poisoning appears rarely in the literature. Ross and Brown (1935) recorded 7 cases with 1 death in a statistical study of poisonings in children at the Toronto Hospital for Sick Children, but they did not describe the cases save to list the death as due to aspiration pneumonia. Harbeson (1936) wrote: "Some people exhibit a decided idiosyncrasy toward turpentine. In these 30 minims will cause vomiting and diarrhea. In larger doses

there is an acute enteritis, vomiting of mucus, which is often bloody, diarrhea and passage of blood-stained mucus. Large doses have a marked effect on the kidneys, causing albuminuria, hematuria, and even complete suppression." His own patient, an infant of eleven months, died in shock a few hours after the administration of 2 teaspoonfuls of spirits of turpentine by the grandmother who "thought the child had worms"—it is really a wonder that any of us are alive.

ACUTE ARSENIC POISONING

Acute arsenic poisoning is not rare, due to the fact that the arsenical pigments are much used in the arts and industries, rat and some fly and roach poisons contain arsenic, and Paris green is extensively used in rural regions as an insecticide. The symptoms usually come on an hour or more after the poison is swallowed, but may appear in a few minutes if the stomach is empty. There is pain in the mouth and esophagus, then in the stomach and entire abdomen. There is nausea and vomiting, often of blood, and early a profuse watery diarrhea. Paralysis of the splanchnic capillaries causes an immense quantity of fluid to escape into the connective tissues; this raises the mucosa into many large blisters and results in large pieces of it being swept away when the fluid bursts into the lumen of the intestine. The abdomen is greatly distended, the colicky pains are very severe and the patient often goes into shock. The stools are of the rice-water type and conceivably might cause some difficulty in differentiating this condition from Asiatic cholera. There is immense thirst, scanty and albuminous urine, and finally suppression of the urine. If death does not come in a few hours to a few days, paralyses of the lower extremities are frequent, as is also fatty degeneration of the liver and kidneys.

THERAPY

The stomach should be washed out with warm water until no more arsenic can be recovered, and then warm milk or other demulcent drink may be given. A large dose of castor oil, or a saline cathartic, is also indicated to flush out the poison perhaps pocketed in the upper part of the gastro-intestinal tract. If no stomach tube is available when the patient is first seen, or if its introduction is impossible or considered to be inadvisable, the emetic drugs should be resorted to, for this stomach must be thoroughly emptied:

Household mustard	1 to 2 drachms (4–8 Gm.) in water.
Ipecac	1 drachm (4 Gm.) of the powder or 4 drachms (15 cc.) of the syrup, in water.
Copper sulfate	7½ grains (0.5 Gm.) in water.
Zinc sulfate	30 grains (2 Gm.) in water.
Apomorphine hydrochloride	1/10 grain (6 mg.) hypodermically for a robust adult, 1/60 grain (1 mg.) for an infant.

The mustard is the least dangerous but also the least effective. The ipecac is uncertain in action and quite depressing. Both copper and zinc sulfates cause vomiting in a very few minutes, and under the conditions obtaining here, *i.e.*, where there are no corrosions of the gastric mucosa, they are not rapidly absorbed and hence are usually not very depressing. However, if they do not cause emesis, further attempt should be made to get them out of the

stomach for the reason that they are very irritant; they are little employed nowadays. Apomorphine is a reliable emetic but it is well known that the after-depression is sometimes great.

The arsenic antidote is kept by the druggist in two bottles, one containing a solution of ferric sulfate, and the other a suspension of magnesium oxide. These are mixed when needed and the freshly precipitated ferric hydroxide is given. The dose of this precipitate is 4 ounces (120 Gm.), but it may be given 1 ounce (30 Gm.) at a time every few minutes for several doses, as it is not poisonous. Clinical observation and impression amply confirm the experimental findings that such slight value as this antidote may have is probably due to its colloidal nature and its effect upon absorption rather than to chemical neutralization of poison; however, Leschke (1934) in his authoritative work on toxicology said he thought we were still justified in using the antidote.

The patient should of course be supported, and the dehydration must be combated by all means possible.

CYANIDE POISONING

These patients are practically always in coma when the physician reaches them. There may be muscular spasms with perhaps even moderate opisthotonos. Respiration is by this time usually very shallow and irregular and the pulse of a very poor quality if perceptible at all; cyanosis is usually marked, the pupils often widely dilated. In many cases the urinary sphincters are relaxed; there may also be froth at the mouth and the odor of cyanide on the breath. Such patients may surprisingly remain alive an hour or more after presenting this picture.

THERAPY

Artificial respiration and oxygen inhalation, gastric lavage with sodium bicarbonate solution, and the usual stimulants are tried in most cases and practically always without results. In recent times, however, the nitrite-thiosulfate treatment, which seems to be favored by the National Safety Council, has come to the forefront of attention; the somewhat newer employment of methylene blue will also be described below.

Nitrite-thiosulfate Therapy.—In this treatment a nitrite is administered systemically to the patient and this is followed immediately by the systemic administration of sodium thiosulfate; the rationale of this therapy probably lies in the conversion of hemoglobin into methemoglobin by the nitrite, the coupling of the cyanide ions to the methemoglobin to form cyanmethemoglobin, which has a relatively low toxicity, and the stimulation on the part of the sodium thiosulfate of the rhodanase conversion of cyanide to thiocyanate. Chen *et al.* (1944), who reviewed 15 cases treated by this combination of nitrite-thiosulfate therapy, 14 of whom completely recovered, suggested the following routine: (*a*) Have amyl nitrite inhaled from the handkerchief for 15 to 30 seconds per minute while two syringes are being loaded, one with a 3 per cent solution of sodium nitrite and the other with a 25 per cent solution of sodium thiosulfate. (*b*) Stop administration of the amyl nitrite and inject 10 cc. of the sodium nitrite solution at the rate of 2.5 to 5 cc. per minute. (*c*) Inject by the same needle and vein, or by a larger needle in a

new vein, 50 cc. of the sodium thiosulfate solution. The injection of both agents may be repeated in half-doses if signs of poisoning reappear.

Methylene Blue.—Hanzlik and Richardson (1934) described the employment of methylene blue in the emergency hospitals of San Francisco as follows: "Inject immediately 50 cc. of a 1 per cent solution of methylene blue (containing 1.8 per cent of sodium sulfate) intravenously; repeat, if necessary, until a total of 200 cc. is injected. Frequently, consciousness and reflexes are restored before the first 50 cc. is completely injected, but if the patient lapses into unconsciousness, or manifests respiratory depression, resume the methylene blue treatment. As quickly as possible, proceed with gastric lavage, using 5 per cent sodium thiosulfate; this oxidizes any unabsorbed poison."

STRYCHNINE POISONING

The presence of strychnine in some of the vermin exterminators has led to instances of accidental acute poisoning in rural regions, but most of the recorded cases, except in children, have been suicidal or homicidal, for the dangerous nature of the drug is so well known as almost to preclude its careless handling. The patients usually say that there is a peculiar feeling at the beginning of each paroxysm, like a slow electric shock that starts above and behind the eyes and sweeps over the whole body; then the spasm begins. The usual position is that of opisthotonos. The spasms last from one-half to five minutes with complete relaxation between. Consciousness is not lost and the suffering is excruciating. Between spasms there is a sensation of approaching death and the patient will plead for someone to hold him, seeming to feel that he is being ruthlessly hurled into oblivion. The usual interval between spasms is five minutes or more, most patients not surviving more than five of these full convulsions; death is either due to asphyxia or to exhaustion. This type of poisoning must be differentiated from the following: *tetanus*, history of antecedent injury, less complete relaxation, trismus (lockjaw) and risus sardonicus earlier, much slower onset and course, much longer interval between paroxysms, absence of opisthotonos; *epilepsy*, clonic spasms, bestial sounds, absence of opisthotonos, unconsciousness, or mania; *eclampsia*, complete unconsciousness during and between spasms, absence of complete opisthotonos.

THERAPY

Initiated clinically by Zerfas and McCallum, in 1929, and subsequently substantiated both experimentally and clinically by numerous observers, the barbiturate treatment of strychnine poisoning has almost completely obliterated the horror with which physicians were formerly wont to view these terrible cases. Below is a condensed version of the barbiturate method, presented by Kempf, McCallum and Zerfas (1933) in reporting 11 cases successfully treated.

(1) Give just enough sodium amytal or sodium pentobarbital solution intravenously to put the patient to sleep or, if in convulsions, to stop them. If using phenobarbital sodium, aim just to stop the convulsions, even though sleep is not induced.

(2) Return of heightened reflexes, complaints about noises, marked response to slight stimuli, or convulsions, call for repetition of the antidote.

(3) Gastric lavage is unnecessary and inadvisable and should be done in no case unless the patient is asleep and there is adequate assistance to prevent injury or aspiration of material from the stomach. Apomorphine should not be given as it increases the latter tendency.

(4) Morphine is not indicated, but quiet dark surroundings are recommended and ether may be used to control convulsions until a soluble barbiturate can be given.

(5) One should distinguish carefully between strychnine action and barbiturate effects before giving second or third barbiturate injections; if in doubt wait for a mild convulsion.

(6) If barbiturates suitable for intravenous injection are not available, give any barbiturate by mouth in dosage not to exceed the equivalent of 15 grains (1 Gm.) of sodium amytal for the adult; *i.e.*, in an amount not to exceed five times the ordinary hypnotic dose, as stated under Insomnia.

POISONS CAUSING STUPOR OR COMA

The types of unconsciousness likely to be encountered in a private general practice, or in the receiving ward of any busy metropolitan hospital, are such as occur in the following states: (1) shock following trauma, burns, hemorrhage; (2) electric shock; (3) sunstroke; (4) eclampsia; (5) diabetes mellitus; (6) hyperinsulinism; (7) epilepsy; (8) hemiplegia; (9) uremia; (10) central nervous system syphilis; (11) extreme cardiac decompensation; (12) extremis in any of the acute infectious diseases; (13) comatose form of pernicious malaria (rare outside the malarial zone, of course); (14) meningeal form of acute miliary tuberculosis; (15) encephalitis; (16) brain tumor; and (17) poisoning. This gruesome band is of very diverse etiology, but all of the entities which come within the province of this book are discussed in the appropriate sections, leaving only the stupefying poisons for us to deal with in this present place. Now of course an individual taking a fatal quantity of any poison will ultimately become unconscious, but there are a few poisons which characteristically induce stupor and then coma so quickly and maintain it so firmly that unconsciousness is the chief symptom and one of the principal things to combat if life is to be saved. Overdoses of ethyl alcohol, morphine or other opiates, chloral, the barbiturates (the first taken excessively in a drinking bout, the other three with suicidal intent usually), and carbon monoxide (inhaled accidentally or purposely in a closed room or garage)—this is the list.

Alcohol.—We are concerned here only with the final anesthetic stages of exceptionally severe acute alcoholism, since the hilarious and stuporous stages of an ordinary intoxication rarely come under observation for treatment as poisoning. The patient is in as deep coma as though chloral had been taken; the pupils are normal or dilated, never contracted. The skin is cold, clammy and pale, the respirations are somewhat slow and stertorous, the pulse is rapid and becomes increasingly weak, reflexes are lost and the temperature is considerably below normal.

Morphine.—The patient progresses gradually from an overpowering sleepiness into a deep coma from which it becomes finally impossible to waken him. The respirations become slower and slower and finally irregular and stertorous, and then they stop; usually the heart has been relatively little affected and

continues to beat for some time after respiration has ceased. In the beginning the skin is warm and moist, but later becomes cold, clammy and cyanotic; the pupils are constricted to the so-called "pinpoint" dimension, but they undergo a terminal dilatation. As death approaches the sphincters relax. Convulsions are rare in adults but are sometimes seen in infants.

Chloral Hydrate.—There is deep narcosis with constricted pupils, complete muscular relaxation, very slow and shallow respiration, barely perceptible pulse, cold clammy skin, rapid fall of temperature and blood pressure.

Barbiturates.—In a severely poisoned patient the symptoms are deep narcosis with constricted pupils, slow and shallow respiration (or perhaps rapid and jerky, depending upon the depth of the depression), rapid feeble pulse, cyanosis, pronounced fall in blood pressure and temperature, depressed or absent reflexes.

Carbon Monoxide.—The patient is comatose and has a peaceful expression, though there is often twitching of the facial muscles; the temperature is usually above normal; the skin is pale, but the lips are nearly always scarlet and there is a scarlet blush on the cheeks and sometimes over the whole body; a brownish-red stippling, much resembling hemorrhagic purpura, is sometimes seen, particularly on the arms. The early symptoms are entirely due to the fact that hemoglobin has a much greater affinity for carbon monoxide than for oxygen, so that the patient is maintained in a state of partial asphyxia. If rescue is effected after only a short exposure (the degree of poisoning depending of course upon the concentration of the gas, the drafts in the room, and many other variable factors), the prognosis for recovery is good, but if profound asphyxia has persisted for very long, recovery does not take place even after all of the carbon monoxide has been released and eliminated; in these cases there has been irremediable brain injury. Many of the late deaths are also due to pneumonia.

THERAPY

Gastric Lavage with Potassium Permanganate Solution.—Alcohol, chloral, or the barbiturates being taken by mouth, it is rational to empty the stomach thoroughly; lavage with warm water is the measure of choice because it accomplishes washing as well as emptying, also for the reason that emetic drugs are very ineffective in these depressed states. If morphine was swallowed lavage is equally indicated, but careful animal study has shown that when this drug has been injected subcutaneously (as is usual in suicide cases) the small amount excreted into the stomach is very doubtfully of any importance in the final outcome; lavage is in great clinical favor, however, even in these instances. Snapper *et al.* (1942) preferred the employment of a nasal tube instead of the ordinary stomach tube, which they believed predisposed to the development of lung complications. A good many years ago the substitution of potassium permanganate solution for plain water in the lavage was suggested on the basis of the well-known oxidizing property of the substance, and such a solution has come to be very much used; accurate information regarding its effectiveness and the best concentration for routine employment is not to hand. The drug is caustic in high concentration and irritant even in fairly dilute solution; perhaps 1 : 5000 is about right, as Hatcher (1935) opined—such a solution can be made by dissolving three of the 1 grain (60 mg.) N.F. VII tablets in a quart of water. Test-tube studies indicate that among those poisons here under consideration, permanganate would be effective only against mor-

phine and a few of the barbiturates (not against amytal, barbital, phenobarbital and neonal, but against alurate and dial and possibly some of the others). Subcutaneous, intramuscular, or intravenous injection of the permanganate is entirely irrational.

Cathartic Measures.—It is usually considered worth while in emergency services to introduce 2 ounces (60 Gm.) of magnesium sulfate in about a tumblerful of warm water before withdrawing the tube, perhaps adding ½ ounce (15 cc.) fluidextract of cascara. If the bowels do not move in a few hours and the patient remains in coma, 1 ounce (30 cc.) of castor oil is sometimes given (the tube is usually still in place in such a case) at four-hour intervals until the peristaltic depression is overcome.

Diuretic Measures.—In view of the excretion of barbital, and to a less extent phenobarbital, alurate and dial, in the urine, intravenous infusion as a diuretic measure has been employed in laboratory studies on dogs. So far the findings of one group of investigators completely contradict those of the other group; clinically the matter has not yet been satisfactorily tested. Comparable studies with chloral, alcohol and morphine have not attracted investigators because of the very slight excretion of these drugs unchanged in the urine.

Stimulants (Analeptics).—A desperate effort is made to rouse the patient from stupor and to combat respiratory and circulatory depression by the use of "stimulants" injected in large doses subcutaneously or intramuscularly: caffeine sodiobenzoate, 7½ grains (0.5 Gm.), or black coffee at body temperature by rectum; metrazol, 1½ grains (0.1 Gm.); coramine (nikethamide), 5 cc.; ephedrine, ⅚ grain (0.05 Gm.); benzedrine (amphetamine), ¼ grain (0.015 Gm.); the employment of heroic dosage of strychnine sulfate, 1/20 to 1/10 grain (0.003–0.006 Gm.) or atropine sulfate, 1/40 grain (0.0015 Gm.) seems to me unwarranted upon the basis of either laboratory or clinical experience.

Picrotoxin was added to the list of injectable drugs a few years ago and has won a favored position for itself; Maloney (1941), reviewing 168 cases of barbiturate poisoning treated with picrotoxin, from the literature and his own experience, recommended the following method of using the drug: give intravenously 1 cc. of a 1:1000 solution per minute until there is a return of the pupillary and corneal reflexes, *avoiding convulsions*. Gold (1943) said that one should discontinue use of the drug at the first signs of some voluntary movement, under no circumstances attempting to restore consciousness with it; the aim should be to maintain a state of mild excitability sufficient to sustain life in order that the patient may be able to excrete the barbiturate. Snapper *et al.* (1942) felt that 5 cc. of coramine, injected intravenously and usually repeated several times, had effected appreciable reduction in mortality in their large experience with opium poisoning in China. As a matter of fact, however, under the variable conditions of practice it is very difficult exactly to assess the value of any of the analeptic agents for they are always used in conjunction with other measures; regarding their employment in carbon monoxide poisoning, Henderson trenchantly remarked: "The less the ambulance surgeon uses his hypodermic syringe on patients with carbon monoxide asphyxia, the better."

Oxygen-Carbon Dioxide.—In carbon monoxide poisoning the patient is likely to be breathing very poorly when found. Artificial respiration must be started at once and continued until the breathing becomes spontaneous. Henderson and Haggard conclusively showed the value of the inhalation of oxygen plus carbon dioxide. In the beginning, 5 per cent of the latter was

advocated, later 7 per cent, which I believe is still looked upon by most men as the ideal concentration, though 10 per cent is advocated by some men of experience. Continuance of this gas treatment beyond one and one-half hours is useless, since by that time practically all the carbon monoxide will have been eliminated.

Reports of the use of oxygen-carbon dioxide in acute alcohol and barbiturate poisoning have appeared. Robinson and Selesnick (1935) found that in alcohol cases death may be prevented and recovery accelerated by inhalation of the 90:10 mixture for a minimum time of one-half hour, but the experimental studies of Newman and Card (1936) and McFarland and Barach (1936), in which both dogs and man were used, did not entirely substantiate these findings. The matter certainly requires further clinical study.

Insulin-Dextrose.—In alcohol cases, Goldfarb *et al.* (1939) found the intravenous injection of 50 cc. of 50 per cent dextrose solution, together with the subcutaneous administration of 15 units of regular insulin, effected an accelerated decrease in blood alcohol; Taylor and Cross (1940) also used this measure with apparently life-saving effectiveness in a child of about four years of age, their dosage being 150 cc. of 10 per cent dextrose intravenously and 10 units of insulin intramuscularly.

Miscellaneous Measures.—It is of extremely great importance to keep these patients well covered and in a warm room because the loss of heat due to peripheral vascular dilatation is very great, especially in alcohol, chloral and barbiturate poisoned individuals. In carbon monoxide poisoning chilling of the body does not occur; indeed, in the beginning there is often an increase in temperature.

Following the report of the resuscitation of patients poisoned with cyanide by the use of methylene blue, it was to be expected that reports of the dye's employment in carbon monoxide poisoning would follow. Several have, indeed, but I believe it is now the consensus that this type of treatment is not only valueless but may even be harmful through further decreasing the oxygen-carrying capacity of the blood.

Purves-Stewart and Willcox (1934) performed lumbar or cisternal puncture and drainage at intervals of twelve to twenty-four hours in serious barbiturate cases; I do not know of anyone else using this method.

The introduction of 4 per cent sodium bicarbonate solution intravenously or by rectum to combat acidosis in carbon monoxide cases is employed routinely by some men, not at all by others.

In carbon monoxide poisoning transfusion of blood in the first hour or two is tempting and is often practiced, but one can only say that upon the whole the results have been disappointing.

ATROPINE, STRAMONIUM AND HYOSCYAMUS POISONING

Rather mild degrees of poisoning with members of the belladonna group are frequently seen in practice; occasionally, also, serious poisoning occurs either in an individual with an idiosyncrasy for one of these drugs or in one to whom an overdose has been given. Where the various plants having this type of action grow wild, or are much used for ornamental purposes, children are now

and then poisoned by eating the berries or seeds, or, as in one of Hughes and Clark's (1939) cases, through ingestion of brews of alleged anti-asthmatic properties made from them. The symptoms are very violent, but the prognosis as to life is good because of the rapid excretion of the poison. In fully developed cases the symptoms are exhibited in two phases: first, difficulty in swallowing, pain in the throat, great thirst, visual disturbances, nausea, redness of face and neck, rise in temperature, rapid pulse, and excitement that goes into delirium and often into mania; second, giddiness, staggering, stupor, respiratory and circulatory collapse.

THERAPY

In Comroe's (1933) case—a patient who had swallowed 7½ grains (0.5 Gm.) of atropine sulfate in solution one and one-half hours before being seen—gastric lavage with large quantities of sodium bicarbonate was performed in the receiving ward and 50 cc. of a saturated solution of magnesium sulfate was placed in the stomach. In the ward it was discovered that paradoxically the patient was suffering from acute pulmonary edema. After phlebotomy of 500 cc. an indwelling catheter was inserted and 400 cc. of urine obtained. When respiration became shallow, carbon dioxide and oxygen were administered. A Jutte tube was passed and 5000 cc. of water given within forty-five minutes, over half of which was vomited; continuous hypodermoclysis of saline solution was begun and cold sponges given in an attempt to reduce the fever. Maniacal outbursts were controlled with 2-grain (0.12 Gm.) doses of phenobarbital. Morphine was not given because of the danger of deepening the late depression; pilocarpine was also withheld in the belief that myoneural junctions poisoned by atropine would not respond to it. The recovery of this p atient, after ingestion of 7½ grains of atropine, probably established a record.

IODINE POISONING

Accidental and suicidal poisoning with this substance is not rare. It is usually swallowed in the form of the official tincture. There are severe gastrointestinal pain, vomiting, diarrhea, hemorrhagic nephritis, and depression and collapse.

THERAPY

Use the emetics (see Arsenic Poisoning) if necessary, but attempt to introduce the stomach tube as soon as possible and wash out with a starch decoction (obtained by boiling in water either laundry starch, rice, or barley) until the washings no longer come away blue. The boiled starch is preferable because it combines more actively with iodine, but lacking it in an emergency, the raw article may be used; try to get some of it down even before the passing of the tube. Sabbatani many years ago advised the employment of a 5 per cent solution of sodium thiosulfate (the plain "hypo" bath employed by photographers is usually a 20 per cent solution) to fix the iodine as sodium iodide; I do not know to what extent this measure has ever been employed. At intervals introduce a demulcent to lessen the gastric irritation, such as eggs, milk, butter, liquid petrolatum. Of course the analeptic drugs (listed in Poisons Causing Stupor) may be used to combat the depression.

WOOD (METHYL) ALCOHOL POISONING

This type of poisoning, that increased so much in incidence in the United States during the first years following the introduction of so-called "prohibition," markedly declined as relatively safe contraband liquor became available and now in the postprohibition era is seen with relative rarity; the victims currently are practically exclusively among renegade vagrants who deliberately drink denatured alcohol. This type of poisoning is characterized by a state of alcoholic inebriety, partially induced by the wood alcohol but largely by the ethyl alcohol also present in the ingested liquor, violent gastric pain and vomiting, disturbances of vision with dilated irresponsive pupils, dyspnea, cyanosis, rapid weak pulse and a period of delirium followed by collapse. If death does not occur in twenty-four to forty-eight hours, there will be partial blindness, which may clear up for a while but is again followed in many cases by total optic atrophy.

THERAPY

The stomach should be washed out frequently by use of the stomach tube, though in the beginning it may be necessary to give a dose of apomorphine hydrochloride, 1/10 grain (0.006 Gm.). This will empty the stomach and somewhat subdue the patient in order that the tube may be introduced. Then as soon as possible give a dose of morphine sulfate by the needle, ¼ grain (0.015 Gm.), in order to lessen the patient's suffering and make cooperation more perfect; if the delirium is wild, 1/300 to 1/200 grain (0.0002–0.0003 Gm.) of scopolamine (hyoscine) hydrobromide may be combined with the morphine. The lavage is to be done with 4 per cent sodium bicarbonate solution, and as soon as possible some of this solution should be introduced into the rectum, thus emptying the stomach and combating acidosis simultaneously. Haggard and Greenberg (1939) have shown that more than 70 per cent of the ingested methyl alcohol is eliminated in the expired air, but some is known to be converted into formic acid, and while it is not certain that this substance causes acute symptoms it very probably contributes much towards the acidosis that is known to be present. Both Merritt and Brown (1941) and Roe (1943) gave their patients sodium bicarbonate intravenously and felt this measure to be life-saving. The latter author found that patients who had drunk large quantities of ethyl alcohol before or after taking the methyl alcohol showed no permanent ill effects, which he felt was due to the capacity of ethyl alcohol to displace methyl alcohol from intracellular attachments, thus checking its oxidation to formic acid; his recommendation that ethyl alcohol be taken rather liberally during the first few days after the consumption of methyl alcohol is therefore logical if a bit heroic.

ACETANILID, ANTIPYRINE AND PHENACETIN POISONING

Acute cases of poisoning with any one or a combination of these drugs are rather infrequently seen nowadays since antipyrine, the most dangerous one of the three, is no longer used in headache nostrums, but a similar type of aniline poisoning sometimes follows the wearing of recently dyed shoes. The

symptoms appear somewhat suddenly and consist of depression and confusion, dyspnea, rapid weak pulse, methemoglobin cyanosis, clammy sweat, cold extremities and a subnormal temperature.

THERAPY

The stomach should be washed out for some time with warm water, and a dose of a saline cathartic should be left in the stomach before withdrawing the tube. Meanwhile try to get the patient warm; support him with stimulant drugs if indicated, and force fluids. Gettler and St. George (1935) said that transfusion is of great value and should be given promptly. There is no specific antidote.

SALICYLATE POISONING

(*Note:* Other aspects of this subject are discussed in Rheumatic Fever)

The general toxic effects of sodium salicylate, phenyl salicylate (salol), acetylsalicylic acid (aspirin), and methyl salicylate (oil of wintergreen) are the same. In most instances the symptoms develop and progress rather slowly but this is not invariable; the most characteristic of them are sweating, hyperpnea, ringing in the ears, dizziness, visual and mental disturbances, increasing stupor, and finally collapse; signs of gastro-intestinal irritation are not invariably present but in some instances they are quite severe and sometimes blood is vomited; in some cases there are several degrees of fever. Bowen *et al.* (1936) pointed out the ease with which this type of poisoning can be mistaken for diabetic acidosis. Mortality is very high; 3 of the 4 cases recently reported by Troll and Menten (1945) proved fatal. Fatalities have followed the taking of 300 grains (18 Gm.) of aspirin, but Hopkins (1945) reported an instance in which 1250 grains (81 Gm.) had been survived; 4 cc. of the oil of wintergreen have killed an infant, 6 cc. an adult.

THERAPY

It is very likely that in efforts directed toward the maintenance of renal function and the combating of dehydration lie the best hopes of saving the patient; on the basis of their animal studies, Dodd *et al.* (1937) felt that if there is fever, attempts to promote the loss of heat, as by alcohol sponging, would also be of value. The experience of MacCready (1943) in three cases strongly suggested the value of prompt and thorough lavage.

Stevenson (1937) reported a very remarkable recovery, that of an infant not seen until twenty-four hours after he had swallowed 15 cc. of oil of wintergreen, being then in extremis with a blood carbon dioxide-combining power of 24.9 volumes per cent, albumin, blood cells, casts and 5+ acetone in the urine. The treatment in this case consisted of gastric lavage with 6 per cent sodium bicarbonate, caffeine and adrenalin injections on admission, blood transfusions, intravenous dextrose and saline, 5 per cent dextrose and solid sodium bicarbonate by mouth, 5 per cent dextrose and 5 per cent sodium bicarbonate (75 cc. of a mixture of equal parts) by rectum, digitalis, colonic irrigations and the forcing of fluids by mouth whenever that was possible.

COCAINE POISONING

The number of fatalities from the use of cocaine is small in comparison with the large number of cases in which the drug is used, even granting that many of the fatalities are not reported; but the number of moderately severe reactions is quite large. Serious cases are of two types: (*a*) The patient seems suddenly to absorb the drug all at once, he gasps, clutches himself frantically, becomes very pale, falls over in a convulsion, and is dead almost before one realizes what is transpiring. (*b*) The events take place somewhat more slowly: the patient becomes very talkative, laughs and cries unnaturally, wants to move about; there is dizziness, irregular pulse and respiration, nausea and vomiting, great abdominal pain, delirium, convulsions, and finally coma and death; the entire process requires several hours. Nowadays of course most of the cases follow the application of cocaine to the mucous membranes, but occasionally they follow the use of some of the synthetic substitutes for cocaine or the accidental employment of cocaine instead of a synthetic substitute in infiltration.

THERAPY

Prevention of Absorption.—If cocaine has accidentally been injected subcutaneously, the quick application of a tourniquet above the site of injection, if this has been in one of the extremities, may be life-saving; the pulse should not be completely obliterated.

Stimulants.—Cocaine is relatively rapidly destroyed, or at least rendered innocuous, by contact with the tissues, therefore anything that will keep the patient alive for a few minutes is of value. Actually, however, the stimulant drugs have not saved many lives, though whatever is at hand should be used (see Poisons Causing Stupor for list). Herzfeld reported some years ago that the ingestion of 1 to 2 ounces (30–60 cc.) of whiskey or brandy, ten to thirty minutes before the employment of cocaine, was very effective in preventing unpleasant occurrences.

Barbiturates.—Based upon the laboratory experiments of Tatum and his associates some years ago, the use of the barbiturates both in prophylaxis and treatment of cocaine poisoning has become quite general. The drug is usually given in ordinary or perhaps slightly larger dosage one-half hour before the use of the cocaine is to begin. In cases in which signs of poisoning have already appeared the soluble sodium barbiturate salts are injected subcutaneously or intramuscularly. Alwall (1941), in Sweden, on the basis of recent experience in 4 cases of acute poisoning, advised the use of a quick-acting barbiturate such as pentothal, because after the preliminary period of great stimulation has passed it is of advantage not to have barbiturate in the blood stream to add to the succeeding period of deep cocaine depression. During the period of stimulation morphine is absolutely contraindicated because it will certainly add to the respiratory depression.

METHYL CHLORIDE POISONING

Poisoning by methyl chloride had been of infrequent occurrence except industrially (Baker, 1927) until there were reported 29 cases with 13 deaths, in Chicago in 1928–1929—all in kitchenette apartments in which there was

discovered a leak in the multiple-unit refrigerator system. A few cases have since been reported in this country (Weinstein, 1937) and in England (Gorham, 1934, and Birch, 1935) among workers in refrigerating and air-conditioning plants. During War II, when freon, which is the usual refrigerant nowadays employed, was preempted for military use, Barach *et al.* (1944) stated that widespread substitution of methyl chloride for freon took place in the maintenance of refrigerating units; but at least up to the time of present writing I have seen no reports of cases of poisoning as a result of return to the agent. The onset of symptoms in methyl chloride poisoning, according to the careful report of Kegel *et al.* (1929), is generally marked by progressive drowsiness, mental confusion, stupor, weakness, nausea, colic and vomiting; some patients experience tremor, hiccup, headache and visual disturbances. The pulse, temperature and respiration are all increased, the pupils are widely dilated, there is anuria and a blood picture suggestive of a primary anemia. Prolonged coma is of common occurrence. Death is always preceded by severe opisthotonic convulsions accompanied by profound cyanosis. A peculiar musty, sweetish odor of the breath is a diagnostic aid. Since methyl chloride is said to decompose in the body into methyl alcohol and hydrochloric acid, the latter quickly transformed into sodium chloride, the result of the chronic exposure to methyl chloride fumes would probably be a syndrome resembling that which might be expected from the chronic exposure to methyl alcohol, namely, effects upon the optic nerves, the hypophysis, the heart, the liver and the kidneys.

The gas is colorless and of such faint odor as to be undetectable in even very poisonous concentration; in 2 instances in Chicago, open windows in the apartment did not protect against lethal doses.

THERAPY

Kegel *et al.* stated that after removal of the patient from exposure the gas is quickly eliminated, and that progressive symptoms in the more severe cases are due to continued injury from oxidation products of the gas until they are eliminated, and to degeneration of nerve cells. In the acute stage, oxygen must be administered until the peculiar odor disappears, even though the patient has to be restrained for the purpose. It is also considered imperatively necessary that sodium bicarbonate be got into the system in any way possible; 500 cc. of Ringer's solution (sodium chloride, 4.5 Gm., calcium chloride, 0.12 Gm., potassium chloride, 0.21 Gm., sodium bicarbonate, 0.15 Gm., distilled water, 500 cc.) given intravenously will further combat dehydration and acidosis. Convulsions may be allayed by potassium bromide, 1 drachm (4 Gm.) in 4 ounces (120 cc.) of water, given as a retention enema, *but under no conditions should chloral or chloroform be given.* Stimulants as indicated. In the subsequent treatment, anemia must be combated.

TEAR GAS POISONING

There is irritation of the eyes, lacrimation, and a tendency toward salivation and irritation of the throat, and slight rubefaction and mild burning of the more tender portions of the skin. Troxel (1942) said that in heavy concen-

trations the bronchi are irritated and that reflex action causes vomiting. When there has been exposure to somewhat more than the usual concentrations encountered when the gas has been employed in instances of mob violence it may require twenty-four hours before the eyes feel perfectly normal again, and it is conceivable that enough irritation of the eyes and throat may occur in such instances to pave the way for secondary bacterial invasion with ensuing conjunctivitis and pharyngitis, possibly sinusitis and otitis media.

When the contents of a tear gas gun are directly discharged against the skin or into the eyes, McNally (1937) found that prompt washing of the skin with 4 per cent sodium sulfite in equal parts of alcohol and water, and the eyes with 0.4 per cent sodium sulfite in 25 cc. water and 75 cc. glycerin, effectively relieves distress.

The substance is not soluble in water and I therefore suppose that the only way to remove it from clothing is by mechanical flushing, *i.e.*, slosh the clothes about for a long time in running water—my own idea, probably worth nothing.

Queen and Stander (1941) reported an allergic skin reaction to tear gas.

STAPHYLOCOCCAL AND SALMONELLA FOOD POISONING

Most individuals poisoned by the ingestion of contaminated foods manifest the following symptoms: abdominal pain, nausea and perhaps vomiting, vertigo and cold clamminess of the skin, and diarrhea often accompanied by considerable tenesmus. Occasionally patients complain of fleeting neurologic symptoms but fever does not usually occur. The incubation period in the common staphylococcal form is usually a matter of only a few hours: of the 141 patients in the outbreak described by Bronfenbrenner (1942), 80 had symptoms within three hours and 61 between three and six hours following ingestion of the meal. Recovery from the severe symptoms usually occurs in eight to twelve hours but the patient often feels quite weakened as a result of the attack for several days. Poisoning with organisms of the Salmonella group is rare in the United States but occurs rather commonly in Europe; the incubation period in this type is sometimes as long as twenty-four hours, several degrees of fever is common and recovery is often delayed for several days. Among the 975 soldiers affected in the outbreak reported by Myers and Eckles (1944) a few had residual symptoms or questionable relapses; in the outbreak of Greifinger and Silberstein (1944) some of the patients continued as convalescent carriers of the organism for as long as thirteen weeks.

THERAPY

The patient's stomach should be completely emptied at once. If he is much nauseated, or has already been vomiting, the introduction of several glasses of warm water into the stomach and then the stroking of the posterior pharyngeal wall with the finger, usually suffices to produce satisfactory emesis; however, one should not hesitate to use the emetic drugs (for a list see Arsenic Poisoning). As soon as the stomach is emptied a cathartic should be introduced: castor oil, 1 ounce (30 cc.); or calomel, 3 grains (0.2 Gm.), to be followed after six to eight hours by a saline cathartic; or magnesium sulfate, or any other saline, in full dose. McRobert (1934), in India, where extensive

experience is had with food poisoning, wrote that he had abandoned the early use of cathartics in favor of kaolin, 2 drachms (8 Gm.) stirred in a glassful of water and sipped as frequently as possible. The patient should be absolutely at rest, take no food, and drink freely of water, hot tea, or lemonade. Two hours after the cathartic has been given the administration of bismuth may be begun: 15 grains (1 Gm.) of bismuth subcarbonate every two hours for 10 doses. The suspension may well be made as follows:

℞	Bismuth subcarbonate	ʒiv	15.0
	Glycerin	℥j	30.0
	Syrup of Tolu to make	℥iv	120.0
	Label: 2 teaspoonfuls every two hours for 10 doses.		

Colicky pain is usually controlled by 2 drachms (8 cc.) of paregoric every two hours for 2 or 3 doses; occasionally it will be necessary to give a single hypodermic of $\frac{1}{8}$ grain (8 mg.) of morphine sulfate, or 1/48 grain (1.3 mg.) of dilaudid, combined with 1/120 grain (0.5 mg.) of atropine sulfate.

These patients are often very much depressed and need support; however, in these cases the following are possibly better to use than the true "stimulants" listed in Poisons Causing Stupor: whiskey, $\frac{1}{2}$ to 1 ounce (15–30 cc.) to be sipped well diluted; aromatic spirits of ammonia, $\frac{1}{2}$ drachm (2 cc.) well diluted.

Feeding with soft foods may be cautiously begun within twelve to twenty-four hours. It is usually advisable to continue the bismuth subcarbonate in doses of 15 grains (1 Gm.) three times daily for several days.

Greifinger and Silberstein (1944) found sulfasuxidine very helpful in the termination of the carrier state in their Salmonella cases.

BOTULISM

Botulism is acute poisoning caused by the toxin of *Clostridium botulinum*, an organism whose spores are widely distributed in nature, being found in the soil, on fruit and vegetables, in dust, in the intestinal tract of herbivorous animals and in the larvae of worms. The disease is caused by the ingestion of a great variety of contaminated animal and plant foods; in the United States principally plant products, in Europe principally meats. Both the bacilli and the toxin are readily destroyed by boiling, but the spores resist boiling for five hours and are only killed by temperatures above 230° F. (110° C.); ingestion of the spores, however, does not give rise to symptoms. Eight per cent brine, or 50 per cent sugar concentration, inhibit the growth of the bacillus and prevent the formation of the toxin. In the latest tabulation I have seen there were listed 367 outbreaks of botulism in the United States between 1899 and 1943; the total number of cases during these 43 years was 1052, the mortality rate 65 per cent. Most of the outbreaks have been due to the ingestion of foods improperly processed at home; it seems that with one possible exception no outbreak has been traceable to commercially canned foodstuffs in nearly twenty years.

Symptoms do not usually appear until eighteen to thirty-six hours have elapsed. At first there is malaise associated with constipation and subnormal

temperature. Gastro-intestinal symptoms are unusual and when they occur are seldom violent. Then dizziness, headache and disturbances of vision appear: scintillation, diplopia, mydriasis, blepharoptosis and loss of the light reflex. Swallowing becomes extremely difficult, the tongue coated and breath foul and the mouth excessively dry, and general muscular weakness comes on. In some cases the patient appears to be completely paralyzed, but in others there are violent paroxysms induced by the attempt to swallow. The pulse is slow, then becomes rapid; breathing becomes labored and death follows from respiratory failure. Most of the victims die within three to six days, but in those who recover there are no permanent sequelae though convalescence is very slow.

THERAPY

The indications here are to empty the gastro-intestinal tract, support the patient, relieve the discomfort and administer the antitoxin.

Emesis and Lavage.—The stomach should be emptied by the use of any of the emetics listed under Arsenic Poisoning. Then a full dose of castor oil or one of the saline cathartics should be administered. This treatment is rational, since the poison has been taken by the mouth, but what can be expected from it is sufficiently indicated in the fact that the symptoms usually do not appear until eighteen to thirty-six hours after the food has been ingested.

Support and Stimulation.—Keep the patient warm and stimulate as indicated (see Poisons Causing Stupor for a list of the stimulants). Maloney's (1939) animal studies indicated that in the very earliest stages of the poisoning picrotoxin definitely increases the severity of the symptoms; after depression has set in the drug may probably be used with safety and good effect. Atropine would only add to the discomfort at any time.

Relief of Discomfort.—The excessive dryness in the mouth and throat can sometimes be lessened by the administration of pilocarpine nitrate, the dose of which is 1/12 grain (5.0 mg.) hypodermically; but the advisability of employing this drug, in view of the sweat and depression that it causes, must be carefully weighed in each case.

Antitoxin.—It has been repeatedly shown by animal experiments that the specific antitoxin is capable of neutralizing *Cl. botulinum* toxin. This antitoxin has for years been available at the Hygienic Laboratory, Washington, D. C., and at the Department of Health of the City of New York; there is now also a Council-accepted antitoxin prepared by Jensen and Salisbury, Inc., at Kansas City, Missouri. The vials of the latter preparation contain 2500 units each of types A and B botulism antitoxin, and the intravenous dosage is said to be not less than 10,000 units to be repeated as indicated by the nature of the case. Geiger (1937) thought there was some advantage in giving the antitoxin in 1000 cc. of 10 per cent dextrose solution, repeating the dextrose infusion without the antitoxin on each of several succeeding days. Watson (1939), of Seattle, being faced with a large outbreak of cases and having no refined antitoxin at hand, used the unpurified combined A and B botulinum antitoxin (labeled for use in animals) manufactured by the Lederle laboratories. First he gave 1000 cc. of 5 per cent dextrose in normal saline with 30 cc. of this antitoxin and 0.5 cc. of epinephrine added, allowing two hours for completion of the injection by gravity flow; later he gave doses of 1500 cc. of dextrose solution with 50 cc. of antitoxin and the epinephrine at eight-hour intervals

until at least 200 cc. of antitoxin had been given; thereafter 25 cc. of antitoxin were given intramuscularly at six-hour intervals preceded by epinephrine. It seems to be the rather general clinical impression that by the time most cases of botulism are diagnosed it is already too late for the antitoxin to be of much value; however, Watson lost only 5 of his 16 patients which is much better than average experience, though one cannot of course draw conclusions from such small numbers.

MUSHROOM POISONING

In practically all cases of mushroom poisoning there are variable degrees of gastro-intestinal disturbance: nausea, vomiting, gastric pain, diarrhea. In addition, depending upon the species of mushroom ingested, there may be any of the following symptoms: nephritis with anuria or hemoglobinuria; jaundice; excessive perspiration, salivation and lacrimation; dilatation of the pupils, mental confusion, excitement, convulsions, coma and death.

THERAPY

The stomach should be emptied by the use of any of the emetics (listed under Arsenic Poisoning), or with the tube. Then a full dose of castor oil or one of the saline cathartics should be administered. Keep the patient warm and stimulate as indicated. Atropine sulfate, 1/100 to 1/40 grain (0.6–1.5 mg.) will act as physiologic antidote if there is sweating, salivation and lacrimation. For the nephritis or jaundice nothing specific can be done. To quiet the excited patient, morphine sulfate $\frac{1}{8}$ grain (8.0 mg.) or dilaudid 1/48 grain (1.3 mg.) may be given, or one may use any of the hypnotics or sedatives (list under Insomnia).

SHELLFISH POISONING

During certain seasons of the year the mussels and clams in some localities contain a powerful neurotoxic poison which causes death by respiratory paralysis in a rather high proportion of the persons affected; Sommer and Meyer (1941), who determined that the poisoning is due to the presence of the dinoflagellate, *Gonyaulax catenella*, recorded that 346 cases had occurred on the Pacific Coast since 1927 with 24 deaths. Cases have also been reported in Japan, Germany, France, Scotland and Norway. Patients who do not have the fatal paralytic form of the disease may experience gastro-enteritis with nausea, vomiting and diarrhea, or they may experience nervous symptoms accompanied by diffuse erythema, urticaria, angina and dyspnea; the latter forms of the malady are usually not fatal.

THERAPY

No specific treatment or antidote for mussel poisoning has been developed. Of course the aim should be to empty the gastro-intestinal tract as rapidly as possible; Sommer and Meyer said that during the 1939 outbreak the provocation of active vomiting by the use of apomorphine was more effective in removing pieces of shellfish from the stomach than lavage. Mussel poison is

strongly adsorbed on charcoal, Lloyd's reagent and similar adsorbents. Alkaline fluids are said to be indicated considering the instability of the poison in an alkaline medium. Of course in severe cases artificial respiration has to be resorted to.

MILK SICKNESS

This is a very old scourge in the United States, having been known apparently to the Indians, but it has never appeared anywhere else. In the early frontier days, cattle browsing in uncleared land and wild pastures were often attacked by a peculiar disease known as "trembles," from which they died, and from which birds and beasts of carrion that fed upon their carcasses were said to have died also. Hull (1941), however, has cast some doubt upon the latter statement for he says that, at least in man, the disease can be contracted only from ingesting milk, butter or cheese from afflicted cattle. Pasteurization of these dairy products is not protective. We now know the cause to be the ingestion by the animals of one or the other of two weeds: white snakeroot and rayless goldenrod. The symptoms in man are: violent vomiting, pain and stiffness in the legs, low blood pressure and extreme weakness, obstinate constipation, swollen tongue, subnormal temperature, coma and a characteristic acetone odor of the body emanations. Mortality is extremely high.

Milk sickness as a human disease is considered practically to have disappeared with the bringing of most of the land in the country under cultivation, but Hardin stated, in 1934, that she had treated more than 100 cases in the preceding sixteen years in North Carolina, Gowen (1938) reported 21 cases occurring in four outbreaks in Illinois in 1936 and 1937, and Hull (1941) stated that there probably occur under normal conditions "not more than fifty cases" in Illinois each year. It is a fact of no little interest that many of the apparently purposeless peregrinations of the Lincoln family during the boyhood of the future President were in reality flights from this blighting affliction. Lincoln's mother, and at least three of his close kin, died of it.

THERAPY

The studies of Bulger, Smith and Steinmeyer (1928), in animals poisoned by white snakeroot, indicated that some of the symptoms might be caused by the marked ketosis, lipemia and profound hypoglycemia which they observed. Hardin (1934) found the administration of dextrose helpful, as also gastric lavage, duodenal drainage and hypodermoclysis of normal saline. She had respect for the custom of the mountaineers to treat the attacks with brandy and honey and found that the majority of patients treated without alcohol in some form died. Alcohol administered to the point of intoxication was the best antidote.

LEAD POISONING

The first symptoms of lead poisoning are usually abnormal fatigue accompanying irritability and sleeplessness, headache, loss of appetite and vague nausea and body pains. Constipation and increasing muscular weakness, espe-

cially of the extensors of the right hand, become marked, and then there appears tremor of the mouth and eye muscles, the latter detectable when the patient lowers the lids. Tremor of the extended fingers usually appears somewhat late, as do also actual radial paralysis and colic. During the colic—which is caused by tonic stimulation of the intestinal musculature by the direct action of the lead so that there is a contraction ring with an area of high pressure due to increased peristalsis above—the severe pains are located below the umbilicus in a scaphoid abdomen, and in contrast to appendicitis and peritonitis there is no tenderness and the suffering is relieved by pressure. The writhing of the intestines is often clearly to be felt. Frequently there is a desire to vomit and to defecate, but very little comes of this; obstinate constipation is certainly the rule, though diarrhea is on record. The patient sweats and the temperature and pulse rate are much decreased; a rise in blood pressure and blood sugar is usual but not invariable. There is also an apparent inability of the vessels to relax, which accounts for the marked pallor and the slow hard pulse as well as the hypertension; this may also give rise to sudden but usually temporary attacks of blindness (the contractions can sometimes be seen in the retinal and conjunctival vessels), occasionally to contracted kidney in protracted cases, to angina pectoris and gangrene of the extremities, and, together with a direct poisoning of the brain cells, to encephalopathy, manifested in hallucinations, babbling, delirium, or stupor. Whether the peripheral paralyses due to lead are of neuritic, muscular, spinal, or vascular causation is not known. Sterility and miscarriage as accompaniments of the malady were recognized many years ago. Death is nowadays unusual but there may be degenerative neurologic sequelae of a most distressing sort, particularly in children, probably as a result of prolonged increase in intracranial pressure. The roentgenologic diagnosis in children is now recognized as possible, but it is my understanding that all pediatricians and roentgenologists are not at one regarding some differential points.

Pallor in this disease is not a direct expression of the anemia, for even in severe cases the red cells rarely fall below 3.5 millions and the hemoglobin below 65 per cent. With regard to stippling of the red cells, one may say: (*a*) There may be stippling which indicates only absorption of lead without clinical poisoning, but, with the exception to be noted, there is no lead poisoning entirely without stippling; the exception, emphasized by the Committee on Lead Poisoning of the Industrial Hygiene Section of the American Public Health Association (1943), is the very acute type of lead intoxication following promptly upon a massive exposure to lead compounds, such as the acute encephalopathy of tetra-ethyl lead poisoning, or the acute and perhaps fatal poisoning that follows the ingestion of a single large dose of a lead salt. (*b*) Belknap (1944), of Milwaukee and a member of the above Committee, said that more than 12 stippled cells per 50 oil-immersion fields (or more than 1000 per million red cells), without an associated anemia and in the face of known lead exposure, often indicates abnormal lead absorption. (*c*) Stippling is not entirely pathognomonic since it may also follow ingestion of silver or zinc and is promoted by potassium iodide and exposure to radium. (*d*) If there is also leukocytosis, the other types of metallic poisoning, benzene poisoning, diseases of the blood-forming tissues and malaria must be ruled out. A moderate lymphocytosis is seen in some cases, perhaps a slight increase in monocytes also. The intensity of the lead line on the gums depends much upon the state

of the mouth. The Committee took the position that abnormal lead findings in the tissues, blood, cerebrospinal fluid, urine or feces mean only that there has been an abnormal lead absorption and thus tend to reveal the existence and the degree of severity of lead exposure, but they do not demonstrate the existence of lead poisoning. However, Ruf and Belknap (1940) felt that findings of 0.15 to 0.2 mg. per liter or over are potentially dangerous for certain cases and call for investigation; Kehoe (1942) said that a urinary lead concentration in excess of 0.5 mg. per liter is a rarity, that above 0.3 mg. it is associated only with grossly dangerous conditions of lead exposure and absorption, and that above 0.2 mg. it does not occur in any other than highly concentrated urines without a definite and significant exposure to lead such as is associated with the admittedly hazardous lead trades; the Committee stated that the large proportion of cases of lead poisoning examined during an episode of intoxication show concentrations between 0.15 and 0.30 mg. per liter. Normal blood lead values were placed by the Committee in the range between 0.01 and 0.06 mg. per 100 Gm. of whole blood with only occasional values in excess of 0.04 mg.; it was stated that findings in excess of 0.07 mg. are indicative of lead exposure within some recent period, while those in excess of 0.10 mg. show that the exposure has been considerable, and findings above 0.50 mg. are open to question as to the accuracy of the determination except in very rare instances of overwhelming accidental exposure. So far as I am aware, the safe level of blood lead which is compatible with a nonhazardous continuation of a given lead exposure has not as yet been adequately determined. Lead storage takes place principally in the calcareous portions of the bones, only secondarily in the liver and kidneys. Jaundice is due to blood disintegration and not to liver damage. A diagnostic point apparently more often resorted to abroad than in this country is the observation of a much increased coproporphyrin content in the urine. So far as absorption, storage and elimination are concerned, it has been shown that the metabolism of lead and of calcium is closely related, but the minutiae of these processes are not yet understood. The question of delayed callus formation in lead-poisoned individuals suffering fracture has been raised, and one school believes that there is injury to the calcium-secreting osteoblasts with actual bone necrosis as a possibility; some, but not all, observers feel that the high incidence of arthritis and analogous conditions also reflects bone injury.

There is much of lead poisoning in the literature of recent centuries. Major, indeed, makes it a truly venerable disease in a delightful historical study in which he proposes one Nikander (second century, B.C.) as "poet laureate of lead colic." Not until the eighteenth century was the entity given scientific status, however, a service performed by Sir George Baker (1722–1809), who got himself denounced as a faithless son of his county for showing that Devonshire colic was due to the lead in Devonshire cider. Today, lead poisoning ranks first among the industrial diseases, and epidemics are also not of infrequent occurrence; in 1930, there were serious outbreaks in two Continental cities whose water is conveyed in lead pipes. Bizarre, indeed, are some of the ways in which we can take harmful amounts of lead into the body, but there is no space here for the list. In infants, the chewing upon painted toys, the crib, etc., is probably the most frequent source. Reznikoff (1943) said that Negroes are much more susceptible to lead poisoning than whites and that alcoholism also predisposes.

THERAPY

After prevention of the possibility of further absorption of lead by whatever means are required in the individual case, the treatment is divided into two periods: the mobilization of lead outside of the blood stream in order to bring about subsidence of acute symptoms, and the promotion of lead elimination.

Mobilization of Lead in Acute Cases.—In the presence of colic or other severe acute manifestations calcium is given because as calcium is stored in the bones lead is stored also, as was shown by Aub, Hunter and their associates, in 1925. Practically instant relief is brought by the very slow intravenous administration of solutions of calcium salts, patients often going at once to sleep though some slight abdominal soreness remains. Evidently there is some antispasmodic action here also. During the period of freedom from pain a full dose of magnesium sulfate is usually given to clean out the relaxed bowel. The calcium injection may be safely repeated if the spasm returns, as it usually does several times in the more severe cases; some men routinely repeat every three or four hours for the first twenty-four to forty-eight hours and three to four times daily for the next two to four days. Calcium gluconate, 10 cc. of 20 per cent solution, is nowadays preferred to calcium chloride, 5 cc. of a 10 per cent solution, for the reason that if it escapes into the adjacent tissues slough will not result (to combat extravasation aspirate as much of the fluid as possible and then inject through the same needle enough sterile 0.1 per cent procaine (novocaine) hydrochloride solution to distend the tissues rather markedly). The injections must be given very slowly—taking four or five minutes—to avoid severe nausea and vomiting; furthermore, rapid administration may cause acute paralysis of respiration and circulation. Even at best there is usually a fall of 10 to 40 mm. in the blood pressure due to peripheral vasodilatation, and the patient feels as though his entire body were on fire. During the time that injections are being given, Belknap also gives 75 grains (5 Gm.) of calcium gluconate in milk three times daily after meals. The diet should be alkaline.

Lacking the facilities for giving calcium intravenously, morphine and atropine must be employed, $\frac{1}{4}$ grain (15 mg.) and 1/100 grain (0.6 mg.) respectively, or perhaps even higher doses; the nitrites are also used, as in angina pectoris. These drugs are much inferior to calcium for relieving colic and of course they do not at all promote lead storage in the bones. If the patient is dehydrated or there has been serious acute infection, dextrose and saline are also given intravenously. Kety and Letonoff (1943) reported the successful control of symptoms in a small group of patients through the administration of sodium citrate, the drug being given in 4 or 5 Gm. doses dissolved in one ounce of water, three or four times daily; 4 patients with severe colic on admission received 50 cc. of a sterile 2.5 per cent aqueous solution by vein. Sodium citrate in this large dosage is extremely disagreeable to take by mouth and so far as I am aware the findings of Kety and Letonoff have not been confirmed.

Elimination of the Lead.—After mobilization of the lead by the above means, the treatment is swung around in the opposite direction, and eliminative procedures are begun; that is to say, a regimen of calcium starvation is instituted. This is best accomplished by giving a calcium-poor diet consisting of clear soups, meats, white and colored (not green) vegetables, macaroni, rice, fruits, and butter and fats as desired (*i.e.*, eggs, green vegetables and milk, even the milk used in cooking and baking, must be eliminated from the diet). In addition deleading agents are given: (*a*) ammonium chloride,

starting with 15 grains (1 Gm.) three times daily during meals (one may either direct that three 5-grain enteric-coated tablets be taken with a meal or that a teaspoonful of a 20 per cent solution be dissolved in a full glass of water and be sipped with the meal) and increasing dosage so that after a week or so 90 to 120 grains (6 to 8 Gm.) are being taken daily; (*b*) hydrochloric acid, 30 minims (2 cc.) of the U.S.P. dilute if the patient can be got to take so much—administering in weak lemonade will help; (*c*) iodine, in the form of 5 to 15 grains (0.3–1 Gm.) of potassium iodide, well given in milk, three times daily, often considerably increased if well borne by the stomach; (*d*) sodium bicarbonate, 5 to 8 drachms (20–30 Gm.) daily, divided into 5 or 6 portions.

Belknap, of Milwaukee, whose industrial experience has been very large, has definite criteria for deleading, as follows: "I do not consider it advisable until all acute symptoms have subsided for a month, until the hemoglobin is 80 or above, until the red blood cell count is four million or over, and until the stipple cells have dropped to 10 or below in fifty fields (from 1,000 to 5,000 per million red blood cells) and have remained there for two or three weeks, and finally until the lead in the twenty-four hour urine is 0.15 mg. or lower. This insures that no great amount of lead is freshly liberated from the skeleton to be superimposed on lead still freely circulating throughout the body.

"For the first two or three courses of deleading, supervision is extremely close in order to note a possible return of symptoms or of the lead line with increase in stipple cells and lead in the urine. If these should reappear I am prepared to fix the lead again in a nontoxic form by high calcium intake. That the lead line does often reappear at first is to me a striking clinical proof of the efficacy of deleading. I do not delead oftener than once in four weeks, and preferably not oftener than once in six or eight weeks, with the first two or three courses of deleading. In this way I avoid the unfortunate consequences of cumulating fresh lead on a preceding tide of loosened lead that has reached its peak at about two to three weeks after stimulation. For the same reason I do not prolong any course of deleading over three or four days. Though I have used them successfully in a few hospital cases I have not yet found it practical to use ammonium chloride and sodium bicarbonate or a low calcium diet to delead men who are actually at work; but it is very easy to give them their iodide drops twice a day, a safe, effective dose being 15 drops of potassium iodide or 7 drops of sodium iodide in saturated solution. Such doses may seem inadequate, but I have found from experience that they just avoid symptoms of actual iodism and that they gently stimulate lead excretion without any recurrence of serious signs or symptoms of lead intoxication.

"Using this technic, I have found that it may take from six to fifteen courses of deleading to free the individual of his most loosely combined and therefore most dangerous lead. After this, further prophylactic deleading or even the acidosis of acute infection usually fails to stimulate an increase of lead in the twenty-four hour urine above 0.15 to 0.2 mg., so that it is unlikely that there will be any recurrent toxic episodes of lead poisoning."

As most of the lead is eliminated through the bowel, the giving of saline cathartics, particularly magnesium sulfate, is considered to be especially important; senna, cascara and other drugs which may cause a more spasmodic type of movement are contraindicated, but later in the treatment mineral oil may be substituted for the salines.

The anginal symptoms and the peripheral vascular spasmodic disturbances are treated with the xanthine diuretics as usual. In the treatment of the paral-

yses, months of patient massage, active movement and perhaps the application of the galvanic current are needed. Some physicians also favor the use here of large doses of strychnine sulfate, 1/20 grain (3.0 mg.) or more three times daily.

Vitamins.—Theoretically, vitamin B_1 (thiamine) might be expected to be of some value in either the treatment or the prophylaxis of the chemical neuritides, but the record does not show it to have been of value in the neuritis of plumbism. Holmes *et al.* (1939) reported that the administration of 100 mg. of vitamin C (ascorbic acid) daily to each of 34 workmen exposed to factory lead hazards and actually experiencing symptoms of lead poisoning at the time resulted in general in an improvement in the blood picture and usually a disappearance of the symptoms of plumbism. However, Evans *et al.* (1943) administered the same amount of ascorbic acid daily to a group of 36 lead workers for one year with the same number of untreated workers as controls and found no reason for recommending the use of this vitamin to minimize the effects of lead absorption.

BENZOL POISONING

Acute benzol poisoning occurs rather rarely. The symptoms are inebriation, salivation, muscular twitchings which eventuate in convulsions, pallor, vomiting, circulatory and respiratory depression, possibly hemorrhages into the tissues, and finally death through respiratory paralysis. But chronic benzol poisoning is assuming a position of some importance in industries in which the workers are exposed for long periods to relatively small concentrations of benzol fumes. In these cases the hemorrhagic tendency is a predominating characteristic, hemorrhages occurring into the skin and all the mucous membranes and in the most severely affected patients even into the serous membranes and the meninges. The patients are very tired and weak, experience nausea and vomiting, headaches, dizziness and sleeplessness. All of the blood components are reduced: there is an almost complete disappearance of platelets, a great fall in neutrophil granulocytes (polymorphonuclear leukocytes), the total leukocyte count falls, there is marked anemia with anisocytosis, poikilocytosis, polychromatophilia and punctate basophilia; it is said that in very severe cases no reticulocytes at all are to be found.

THERAPY

In cases of acute poisoning the patient is of course to be got out into the fresh air as soon as possible and he must be given artificial respiration and oxygen-carbon dioxide and the analeptic drugs are to be employed (see Poisons Causing Stupor). Leschke (1934) said that if the poison has been taken by mouth it is of value to wash out the stomach with a 3 per cent suspension of animal charcoal followed by the free administration of animal charcoal and magnesium sulfate solution by mouth. In the chronic cases the patient is put to bed, given a full diet, and transfused with whole blood as often as seems practicable. Liver and iron are also given in large amounts. Wilson (1942) recommended in addition large daily doses of calcium, phosphorus, yellow bone marrow and multiple vitamins. In the belief that the spleen has inhibiting effect on the bone marrow, splenectomy is sometimes resorted to in desperately ill patients, but I am unable to cite any statistical evidence of its efficacy.

PHOSPHORUS POISONING

In lands, particularly in the Far East, where the sale of matches made from yellow phosphorus is still permitted, most cases of phosphorus poisoning are due to the chewing of matches by children, but in the United States practically all of the cases result from the ingestion of roach or rat paste or fireworks. This type of poisoning is not frequently encountered in our country; still, LaDue *et al.* (1944) reported that 16 patients had been treated for phosphorus poisoning in Charity Hospital in New Orleans since 1920, 4 of whom died. In most instances the presence of severe abdominal pain, emesis, possibly diarrhea, an odor of garlic on the breath, icterus, ecchymosis, coma and convulsions, combined with a history of the ingestion of phosphorus and the recovery of phosphorus from the luminous vomitus or stools, makes diagnosis easy; in the absence of a history of the ingestion of vermin or rat poison or fireworks, however, the cases can be quite baffling. The liver is usually enlarged and the blood sugar level is low as a reflection of failure of glycogenolysis; in Chretien's (1945) patient the white cell count fell to 1200. The symptoms in phosphorus poisoning may appear within a few hours or not until several days after the poison has been taken.

THERAPY

The stomach must be lavaged of course as soon as possible; it is probably wise to employ 1:5000 potassium permanganate solution for the purpose since this agent will convert yellow phosphorus into harmless phosphates. Since Atkinson showed in experimental studies a number of years ago that the administration of liquid petrolatum either before or after feeding phosphorus would save experimental animals through solution of phosphorus in the oil, it is probably advisable to leave several hundred cubic centimeters of liquid petrolatum in the stomach after completing the lavage.

In every case of course it must be assumed that some absorption has taken place; therefore one must attempt to protect the liver and the kidneys, which are the organs most severely damaged by the phosphorus. In a very severely poisoned patient who recovered, LaDue *et al.* (1944) gave 2000 cc. of 10 per cent glucose intravenously immediately after completing the lavage and repeated this at least once daily for the first ten days. An eggnog mixture containing 60 Gm. protein, 300 Gm. carbohydrate and 30 Gm. fat was also given each day by duodenal intubation, vitamin concentrates and 2 oz. of mineral oil also being given. After ten days the patient was able to eat and was placed on a diet containing 450 Gm. of carbohydrate, 120 Gm. of protein and 70 Gm. of fat (diet tables in Diabetes).

SNAKE BITE

The total number of deaths annually throughout the world from the bites of poisonous snakes is probably between 25,000 and 35,000, of which 20,000 to 25,000 occur in India alone. The other cases are scattered throughout all the rest of the world, few regions being without one or more dangerous families of snakes; Europe, however, is relatively free, perhaps no more than 2 or 3

fatal cases occurring there each year. The chief snakes according to their distribution are: *Asia*, the several vipers, the daboia, the habu, the cobra, the king cobra, the krait; *Africa*, the vipers, the puffadder, the asp, the mamba; *Oceania*, brown snake, black snake, copperhead, taipan, tiger-snake, death-adder; *Europe*, the vipers; *North America*, the vipers, the water moccasin, the copperhead, the rattlesnakes, the coral or harlequin snake (southeastern United States); *Central and South America*, the vipers (the fer-de-lance inflicts most of the serious bites in Central America, but the bushmaster, a heavier viper, bears a worse popular reputation), the copperhead, the water moccasin, the rattlesnakes, and the coral snakes, the latter also occurring in the West Indies.

The symptoms of poisoning vary with the different snakes; I have drawn freely upon Amaral for the following descriptions. *Cobra:* local burning, edema and congestion; prostration; nausea, vomiting, salivation, cold sweats; rapid and weak pulse, rapid and later slow and weak respiration; difficulty in speech and progressive muscular paralysis; respiratory death. *King cobra:* little or no local reaction; difficult and stertorous respiration; patient remains in a semi-conscious state until death from respiratory paralysis. *Krait:* rapid emaciation, progressive muscular weakness and other symptoms of slow intoxication; death after six or more days from respiratory paralysis. *Daboia:* intense local reaction, ecchymosis and hemorrhages; nausea, vomiting and collapse with rapid weak pulse; if death is not immediate, hematuria and albuminuria, anemia, intense emaciation, and then death. *Fer-de-lance, habu:* immediate local edema which spreads rapidly, ecchymosis, severe pain and hemorrhage at site of bite; parched throat, thirst, congestion, hemorrhages (except following the bite of the habu) into the mucous membranes and even through the skin, albuminuria, death in toxic exhaustion (habu causes respiratory paralysis). *Rattlesnake:* local pain, hemorrhage, ecchymosis, gangrene; rapid general symptoms (I once saw a young Negro lad vomiting and profusely sweating twenty minutes after I had seen him bitten by a large diamond back) consisting of rapid and weak pulse, nausea, and vomiting, sometimes diarrhea, cold sweats, and a series of collapses until early death takes place. The pygmy rattler and the American copperhead do not seem to be among the most poisonous snakes; also a bite by the true water moccasin (not the maligned, though vicious, common water snake) is quite rare. *Coral:* no local evidences except intense pain, salivation and lacrimation; depression, somnolence, convulsions, death in collapse. *Tiger, death-adder, brown, black, taipan:* regarding this group of snakes of Australia and the Southwest Pacific, Kellaway (1942) wrote that there is nausea and vomiting, blanching of the skin and sweating, drowsiness, rapid shallow pulse and respiration, many neurotoxic symptoms except in the case of the black snake, such as drunken gait, slurring speech, etc., sometimes haemoptysis, haematemesis and haematuria, and death from respiratory paralysis sometimes following convulsions.

THERAPY

Immediate Surgical Treatment.—Apply a tight bandage above the knee in bites on the lower extremity, above the elbow in bites of the upper extremity; release for a few seconds at ten- or fifteen-minute intervals in order to prevent gangrene below the level of the tourniquet. Traditionally it is the custom, as soon as the tourniquet has been applied, to enlarge the wound with crucial incisions 1 inch or more across and begin sucking out the venom, sucking for

alternate fifteen-minute periods for many hours, the tourniquet having been removed after eight hours. However, Clark (1942), discussing his experience of snake bite during many years in Central America and regions contiguous to the Canal Zone, said that such incisions are unlikely to expose the areas in which venom has been deposited since the fang is curved and the deposition of venom is not made directly beneath the fang marks; furthermore incisions which do happen to pass through venom droplets only increase the areas of raw surface through which rapid absorption may take place. Clark advocated simple vigorous sucking of the wound for five-minute periods at frequent intervals and removal of the tourniquet one hour after the antivenin has been administered. The application of caustics or antiseptics to the wound site is no longer advised.

Antivenin Treatment.—Obtain the antivenin at once and inject half of an ampule subcutaneously around the site and the remainder intramuscularly—in fulminating cases intravenous injection is permissible. Doses are doubled for children because the smaller the body the greater the proportionate amount of venom in the tissues. Repeat injections at one- to two-hour intervals unless and until symptoms are markedly diminished.

In North America.—The serum is polyvalent against the venoms of rattlesnake, water moccasin and copperhead. It is marketed in 15 cc. vials and is known as "Antivenin (Nearctic Crotalidae) Polyvalent." The problem of getting this antidote to the victim, who has probably limped into some isolated village, is of course a difficult one; however, it is believed that in time numerous stations will be established near regions badly infested by poisonous snakes, which, when reached by telephone, will send out a supply of the serum in an airplane and drop it over the place from which the call was sent. The feasibility of this plan has already been shown in the region around San Diego, California, the point of telephone call being the zoological garden in that city.

In Central America.—The serum, known as "Antivenin (Bothropic)," is being extensively and effectively used in Central America since the development of the snake farm for collection of venoms at Tela, Honduras. Clark (1942) said that it is effective against the bites of all the more usual poisonous snakes of the region except the tropical rattlesnake, the bushmaster and the coral snake.

In Oceania.—Kellaway (1942) stated that the antivenin available in Australia is a monovalent one prepared by the use of tiger snake venom, but that it is so potent as to be useful in treating the bites of most of the Australian snakes except the brown snake.

In India.—Despite the fact that Calmette's serum seems to be absolutely antidotal to cobra venom, its use can hardly have made even a faint impression on the mortality record in India. The working people, scattered in isolated villages over an enormous territory, often sleep out at night and thus fall easy victims to the wandering cobra that, seeking its meal of snakes, finds the sleeping native and wantonly bites him. There is little hope that serum will ever be sufficiently well distributed that its administration will become possible to many of these unfortunates soon enough to save their lives.

In South America.—We know practically nothing, of course, of the incidence of fatal snake bite in the wilds of this continent, but on the large estates and industrial workings the conditions are more favorable for treatment than in India. The working population, while scattered through the forests, particularly in the north, is more or less concentrated about the haciendas, making it

easy to see the victims promptly and provide efficient care; it has been stated that the antivenins are being used successfully under these circumstances.

In England.—The experiences of both Batt (1944) and Williams and Davies (1945) indicated that in England an antivenin effective against the venom of the English viper is not readily available.

Novocaine Block.—Taoubes (1941), in Russia, thought that circular novocaine block rendered the nervous system insusceptible to the action of the venom of the European viper in the 12 cases he treated. From 100 to 200 cc. of 0.5 per cent solution of novocaine was injected subcutaneously to effect a circular block either around the upper third of the upper arm or the upper third of the thigh, depending upon the site of the bite.

General Supportive Measures.—Since the symptoms in seriously poisoned patients are much like those of shock, with peripheral vascular relaxation, and accompanying dehydration and alkalosis from the vomiting and diarrhea, the administration of saline intravenously is indicated. Such treatment will also possibly serve to dilute the toxin. Blood transfusion and oxygen administration is indicated. The use of alcohol seems to lessen the patient's chance of recovery, popular opinion to the contrary notwithstanding.

SPIDER BITE

In the United States practically all of the authenticated cases of arachnidism have been due to the bite of *Latrodectus mactans*, commonly known as black widow, shoebutton, hourglass, and T-dot spider. To Bogen is due great credit for reawakening interest in this subject, for it is only since he made his series of reports some years ago that the profession has become fully aware of the frequency of spider bite and the nature of the syndrome. Most of the victims have been males who were bitten on the penis or adjacent parts while sitting in an outdoor privy. The stinging pain of the bite soon subsides and there is usually little or no visible lesion; then, fifteen to thirty minutes later, pain reappears, usually at the site of the bite and spreads all over the body, reaching its maximum about an hour after the bite. There is generalized muscle spasm and very often a boardlike rigidity of the abdominal wall. The pain is agonizing but local tenderness is usually entirely absent; the patient usually sweats profusely, is restless and anxious, and may exhibit spasmodic twitching of the muscles of the extremities, priapism, localized edema and urinary retention. There may be a mild rise in temperature accompanied at times by a slow pulse; the blood and spinal fluid pressures are usually above normal.

The vast majority of the victims of this spider recover in a few days but in occasional instances paresthesias and muscular spasms and weakness persist for several weeks or even months.

THERAPY

The acute symptoms of spider bite are so severe as to necessitate immediate efforts at alleviation. Resort is practically always had to the opiates, though all observers agree that these patients can tolerate very large amounts without deriving much relief from them. Hot baths are often found helpful; Blair (1934), who permitted himself to be experimentally bitten, obtained his best

relief in this way, and Walsh and Hargis (1935) found baths very useful in their series of cases. Magnesium sulfate, given intravenously, was reported to be very helpful by De Asis (1934), treating "Red back" (*Latrodectus hasseltii*) spider bite in the Philippines; Frawley and Ginsburg (1935) used the drug with much satisfaction in California where our own "black widow" had been in attendance—20 cc. of 10 per cent solution, repeated as necessary to overcome spasticity and hypertension. Gilbert and Stewart (1935) reported immediate and striking relief from the intravenous administration of 10 cc. of 10 per cent calcium gluconate; Mason (1938) had a similar experience, giving the injections repeatedly during the several days during which attacks of pain recurred in his patient. The use of convalescent serum has not given consistently good results nor has spinal drainage. Sampayo (1943), in Argentina, developed an antitoxin very effective against experimental poisoning in animals, but I have seen no record of its employment in the human. Bogen felt, and others have expressed themselves in agreement with him, that the stimulant drugs and alcohol should not be used, and furthermore that there is no rational indication for local treatment of the site of the bite other than the simple application of an antiseptic such as tincture of iodine.

POISONING TREATED ELSEWHERE IN THE BOOK

The places throughout the book in which the toxicology of various drugs is dealt with are too numerous to list here. The reader is requested to look in the Index for the drug in which he is interested.

BURNS, SHOCK, CRUSH AND BLAST SYNDROMES

BURNS

In the years since the outbreak of War II there has been much experience with burns and consequently an extensive reexamination of the principles of therapy; it is now possible to present the subject in a rationalized and much simplified manner.

GENERAL CARE IN MAJOR BURNS

Pain, Fear, Cold, Exhaustion.—The recently burned individual will most likely be suffering very severe pain, he will have had a great fright and may still be in a very fearful state, and if he has been involved in a general holocaust he may be in an exhausted condition and perhaps thoroughly wetted incidentally to the efforts of the fire fighters to control the conflagration. Of course the patient should be got into comfortably warm surroundings as soon as possible, but the newer studies have shown that the use of heat for its own sake may actually be harmful since the patient with the cold extremities of shock may be merely manifesting the compensatory phenomenon of conservation of blood volume for the vital centers; to attempt to warm up such a patient and produce vasodilatation may do serious harm. Burn tents with batteries of electric light have practically disappeared from hospitals, at least in this country.

Morphine should be given as soon as possible to relieve the fright and especially the pain, but Lam (1944) pointed out that excessively large dosage may not be more effective than moderate dosage though it carries with it the danger of respiratory depression. Beecher (1944) made the valuable observation from his experience in the North African theater of operation that men given large doses of morphine when in severe shock showed signs of morphine poisoning after receiving shock therapy, the reason being that when no relief occurred following the use of the first half-grain hypodermic injection it would be followed by a second or even a third over a period of two hours, and then when restoration of blood volume and blood pressure caused restitution of the peripheral circulation and rapid absorption of all the injected morphine the symptoms of poisoning resulted. Beecher (1943) also developed the point, in his account of the handling of the victims of the Boston Cocoanut Grove fire, that one should not attempt to treat the restlessness or mania due to anoxia with morphine. If morphine is to be given to an individual well advanced in shock it is perhaps well to give it cautiously intravenously, employing $\frac{1}{8}$ to $\frac{1}{6}$ grain (8 to 10 mg.) dosage and repeating at fifteen- or twenty-minute intervals until the desired effect is obtained. To combat fear and hysteria sodium pentobarbital may also be given intravenously in a dose of $1\frac{1}{2}$ grains (90 mg.), or 2 to 4 cc. of paraldehyde may be given intravenously.

Gordon (1943) reported his extremely interesting experience in the use of procaine (novocaine) intravenously for control of pain in burned soldiers in War II. Ten patients were so treated, in most instances receiving 300 cc. of an infusion of 0.2 per cent novocaine and 5 per cent dextrose over a period of

forty to sixty-five minutes; they were reported to have experienced practically no pain during the dressing and to have remained comfortable without morphine or any other analgesic for the succeeding twelve hours.

Plasma Loss (Shock).—In a few instances pain apparently provokes an imbalance of the autonomic nervous system resulting in relaxation of vascular tone, an increase in the capacity of the vascular bed and a resultant drop in blood pressure. This "primary" shock is usually effectively combated with rest, warmth and morphine, but the "secondary" shock, which comes on a little later, requires to be combated with some sort of replacement therapy. The mechanism of secondary shock seems to be the following: as a result of the injury to capillaries through the burn there is a loss of plasma both into the burned tissues and by "weeping" from the skin, and later there may be generalized loss of plasma in the tissues remote from the burn site; the total loss may exceed several liters in a very short period of time. Secondary shock, then, is a state characterized by reduction in blood volume, cardiac output and blood flow, and hemoconcentration, and carrying with it the threat that the resultant anoxic damage to tissues will, as a result of its persistence, give rise to generalized increased capillary permeability of an irreversible type. Secondary shock must be most vigorously combated.

Plasma.—As experience stands at the time of writing, in early 1945, there is not much doubt of the value of the early administration of human plasma in these cases. Harkins' (1944) rule for determining dosage is that for every point above the hematocrit normal of 45, 100 cc. of plasma should be given to an adult of 150 pounds (70 kg.), the dosage being reduced proportionately for children. Harkins also suggested a simpler rule, namely, that 50 cc. of plasma should be given for each 1 per cent of the body surface that is burned; this rule may also be expressed as follows: 1 pint (500 cc.) of plasma for each 10 per cent of body surface burned. Percentage of body surface is usually derived from the following table devised by Berkow a good many years ago:

Region	*Per Cent of Body Surface Involved*
Head	6.0
Upper extremities:	
Both arms and forearms	13.5
Both hands	4.5
Total	18.0
Trunk:	
Anterior surface	20.0
Posterior surface	18.0
Total	38.0
Local Extremities:	
Both thighs	19.0
Both legs	13.6
Both feet	6.3
Total	38.9

There are other methods of determining the amount of plasma to be used but they are all more complicated than those of Harkins. The plasma, which is to be given intravenously of course, should be administered in divided doses; the distribution between the individual doses will have to be decided in each individual case, but Johnston's (1944) method serves well as a rough guide: give $\frac{1}{3}$ of the calculated quantity in the first two hours, the next third in the

following four hours and the remaining fraction in the last six hours. When possible, repeated hematocrit studies should determine the necessity for further administration of plasma, remembering that the danger of secondary burn shock persists for thirty-six to forty-eight hours in most instances.

Sodium Lactate.—Rosenthal (1943) showed in animals that large amounts of isotonic electrolyte solutions taken by mouth were very effective in the control of burn shock. Fox (1944) employed sodium lactate solution with great satisfaction in a series of 23 severe third-degree burns; he admitted that isotonic sodium chloride would have been a more physiologic solution but employed the sodium lactate because it had been shown to be slightly superior to other sodium salts in Rosenthal's experiments. The agent was given in 1.75 per cent solution, at which it is isotonic, by mouth at once and repeated at fifteen-minute intervals on schedule so that approximately 7 to 10 liters (from 10 to 15 per cent of body weight) of the solution are administered within the first twenty-four hours. Vomiting, which frequently occurs in severe burns, was treated by administration of more fluid; frequently a small Levine tube was passed through the nose and the sodium lactate solution was administered by continuous drip. If the fine results obtained by Fox can be confirmed by others (after his original paper Fox *et al.* brought the series of cases satisfactorily treated up to 64), it would seem that a great simplification in the combating of burn shock has been accomplished.

It is routine practice in many hospitals to give to the burned patients whose epidermis is broken a prophylactic dose of tetanus antitoxin or a booster dose of tetanus toxoid if he has previously been immunized.

Adrenal Cortex Extract.—In their early studies Rhoads *et al.* (1941) felt that through treatment with adrenal cortical extract they could promote a rapid return to normal capillary permeability in burned patients, but in a more recent publication (Rhoads *et al.*, 1943) these workers reversed their earlier opinion; the bubble of cortin in burns therefore seems to be exploded.

Dehydration.—In addition to replenishing the plasma volume water must be given to maintain kidney function. Cope (1944) said that 1500 cc. should be given in the first twenty-four hours and 1000 cc. in the second twenty-four hours, and that if the patient is thirsty on this quantity of water it may be necessary to give some physiologic saline solution parenterally; but he warned that water must be given very moderately and cautiously during the period of resorption of edema fluid, since several cases had been reported to him in which there was evidence of increased plasma volume and venous pressure, in addition to signs of pulmonary congestion between the third and fifth days after the burn, in patients who had received large quantities of parenteral fluid therapy beyond the third day.

Asphyxiation.—In some instances anoxia will be the result of carbon monoxide poisoning but usually it results from pulmonary injury consequent upon the inhalation of flame, smoke, or superheated air. Apparently many of the deaths in the Cocoanut Grove disaster were due to this complication. Of course the administration of oxygen-carbon dioxide is obviously called for and when it can be administered it brings quick relief and quiet. However, many of these patients may be rendered so maniacal by their suffering that they cannot easily be sufficiently quieted to make the administration of oxygen feasible, and in other instances the lungs fill up with fluid so rapidly that no treatment is life-saving. Beecher (1943) reported that 5 tracheotomies were performed in 39 of the Cocoanut Grove patients; 3 of the 5 patients died.

Infection.—The measures to be taken in the protection of the burned area are later described in the section on the local treatment of burns, but despite the utmost precautions it is probably well to assume that all burns are contaminated and may become infected. On the basis of his experience in the Cocoanut Grove fire, when all burned cases were given parenteral chemotherapy with what were felt to be excellent results, Cope (1944) stated that chemotherapy either by mouth or intravenously is indicated for all burned patients except those with first-degree or other burns of small extent in which the epidermis is intact or in which it is anticipated that the blisters of a second-degree burn will not rupture. Penicillin may be expected to prove the ideal drug since it controls the staphylococcus as well as the organisms susceptible to sulfonamide action, but at the time of this writing, early 1945, no reports of its employment on a large scale in the treatment of burns have yet been seen. Sulfadiazine therefore remains the drug of choice. Cope said that in severely burned patients with ruptured epidermis the drug should be started early by the intravenous injection of 2.5 Gm. of the sodium salt, subsequent doses being given either intravenously or by mouth in quantities adequate to maintain a blood level between 6 and 12 mg. per 100 cc. He said that, barring toxic reactions, such chemotherapy should be continued until the wound is covered with epidermis firm enough to bar the entrance to organisms. A contrary report regarding the efficacy of sulfadiazine in the prevention of infection is that of Meleney (1943), who concluded that the cases studied in a number of National Research Council projects did not indicate that routine employment of this agent systemically was effective in preventing local infection.

Abnormal Metabolism.—There is every likelihood that azotemia and acidosis will result if the state of shock is very prolonged; the preliminary studies of Taylor *et al.* (1944) indicated that marked hyperglycemia associated with a high rise in the blood lactic acid, both probably being obtained at the expense of the carbohydrate reserves of the body, may also be expected. Fluids, perhaps sodium bicarbonate and dextrose, may have to be given intravenously, but the matter of chief importance is to relieve the shock through plasma replacement. Cope (1944) seemed to be in agreement with the generally held opinion that vitamin B is rapidly dissipated and that the administration of thiamine hydrochloride is therefore quite rational.

Blood Loss.—In severely burned patients with infected wounds the need of repeated blood transfusions will be indicated by the fall in hematocrit due to the decrease in the number of red cells, but Cope (1944) pointed out that one must be careful to differentiate this fall in the hematocrit reading from that due to hemodilution which occurs during the period of resorption of edema fluid, for in the latter case rigid restriction of fluid intake, rather than transfusion, is indicated.

Nutrition.—Burned individuals frequently lose a great deal of protein through necrosis and exudation, and if they have a long siege of grafting operations they often lose their appetities. Such patients may become seriously edematous as a result of the low plasma protein level. Taylor *et al.* (1943) reported a case in which they accomplished a daily intake of 500 Gm. of protein by feeding a high protein, high calorie, high vitamin diet by stomach tube and giving intravenous amino acids, plasma and human albumin; in addition 30 to 40 Gm. of brewers' yeast were given, and 20,000 units of vitamin A, 100 units of vitamin D, 200 mg. of ascorbic acid, 20 mg. of riboflavin and 200 mg. of nicotinamide.

LOCAL TREATMENT OF MAJOR BURNS

Cleansing.—If the burned patient is still clothed, Allen and Koch (1942) advised that the adherent burned clothing be soaked off in a tub of clean water maintained at a temperature slightly above that of the body, the patient having of course been given a preliminary dose of morphine. It is the frequent practice thereafter to débride the wounds—*i.e.*, to open all unruptured blebs and cut away the dead epidermis overlying these blebs and those that have already ruptured—and then gently to wash the wound with soap and water and rinse it with saline solution. During this procedure the utmost aseptic precautions are to be taken and the surgeon and his assistants are to wear sterile gowns and gloves and gauze masks. In this country many men employ lard for removing oil and grease, the remaining lard on the skin being easily washed away with soap and water; in England a cream containing 0.75 per cent of cetyl trimethyl ammonium bromide (CTAB) is much employed for this purpose, Colebrook (1943) maintaining that this agent is an effective disinfectant as well as detergent. As a matter of fact, however, there is great objection to this whole initial cleansing procedure since the maneuvers are often exquisitely painful, tend to aggravate shock, and indeed may require the administration of a general anesthetic in order to permit their accomplishment. Furthermore, it has not been established that unopened blebs become infected, or that the dirty undébrided open wound surface is any less likely to become infected, after a thorough cleansing than without. The victims of the Cocoanut Grove disaster treated at the Massachusetts General Hospital were not given any preliminary cleansing at all, and Cope (1943) reported that the staff was convinced that excellent results had been obtained.

Compression Bandage.—After completion of the initial cleansing of the wound, or preferably according to the opinion of many men at once upon seeing the patient and without any preliminary cleansing at all, the burned area is covered with sterile petrolatum or boric acid ointment (the latter seems currently to be losing popularity because of the possibility of absorption of boric acid) and a single layer of fine mesh sterile gauze strips is applied, or the ointment may be applied to the gauze first. Over the petrolatum gauze is then laid half a dozen layers of flat dry sterile gauze, over this a mat of gauze fluff and over the fluff sterile mechanics waste or sea sponges, the latter to provide under the retaining bandage a resilient covering that produces an even pressure over the injured part without causing constriction; an elastic bandage is then applied with firm pressure over the entire dressing to hold it in place. This dressing is not changed for ten to fourteen days and when a new one is put on the utmost aseptic precautions must be observed, *i.e.*, all concerned in the changing of the dressing are to be scrubbed, gowned, gloved and masked as for a major surgical procedure.

There is practically universal testimony both in the armed forces and in civilian practice to the superiority of this compression bandage type of treatment to any that has heretofore been used in extensive burns. Indeed, McClure and Lam's (1943) statistical study of minor industrial burns found the method superior to all others even for individuals who remained ambulatory.

Casein Modification.—Curtis and Brewer (1944) devised a modification of the compression bandage treatment in which before application of the bandage a specially prepared casein solution is applied over the burned area with a sterile wooden spatula and the area covered with a sterile flexible trans-

parent film and then the bandage applied. They obtained very gratifying results in a series of 165 cases of burns of varying severity, but as yet I have seen no confirming report.

Plaster Casts.—In recent years a number of surgeons have been employing plaster casts in the treatment of burns, the technic of application varying widely. Perhaps the method of Levenson and Lund (1943) is that most used: one layer of sterilized fine mesh petrolatum gauze is applied to the skin over the whole area to be covered by plaster, fitting it exactly, and carefully placing it between the fingers in burns of the hand. This layer is covered with four layers of sterile open mesh gauze, fitted carefully without overlapping and, in burns of the hand, surrounding the thumb but not going between the fingers. Very thin plaster slabs are then moistened and molded over the extremity front and back, a thin layer of rolled plaster then completes a nearly skin-tight, light, well-fitting plaster which extends 3 to 4 inches above the burn; the fingers are placed in a semiflexed position. This original cast is left in place for fourteen days and if the burn has not healed at the time of its removal another is applied at once and left on for a further period of fourteen days. The plaster cast has not as yet been used as much as the compression bandage and some time will be required to determine whether it is equally as satisfactory as the latter.

Discarded Agents.—In the revolution in burn therapy which has been recently effected the coagulants have been discarded because they produce actual damage in the denuded area and tannic acid, long one of the most popular of them, has been shown at times to promote infection and to be responsible for central liver necrosis. The use of the dyes has been given up because they do not seem to reduce the number of infections and possibly are responsible for some delay in wound healing. The local use of drugs of the sulfonamide series has not prevented infection in burns, but it has sometimes given rise to excessively high sulfonamide blood levels and in sensitive individuals has not infrequently superimposed a toxic dermatitis on the burn. It might be expected that penicillin will be more effective locally, and indeed it has been shown to be, but it quickly loses its effectiveness and the necessity to make reapplication at twenty-four-hour intervals would necessitate the complete discarding of the new compression technic. Methods employing one or another type of continuous saline bath seem now to be completely outmoded.

LOCAL TREATMENT OF MINOR BURNS

As stated above, experience in industrial practice has shown that the average minor burn is best treated by a small compression bandage. For even more minor "household" burns, Aylwin-Gibson (1943) stated that she had learned through many years' experience that malt vinegar quickly and lavishly applied is the most effective of all agents both for relieving pain and preventing blistering. Levine (1943) found hexene-ol, a fatty alcohol discovered in the development of synthetic rubber, very satisfactory in a series of 238 minor burns; the agent effected prompt and lasting relief from pain, prevented the formation of blisters, and itself caused local irritation in less than 1 per cent of the cases in the series; it did however produce localized perspiration and Levine therefore felt that it was not advisable to treat extensive burns with it since the promotion of much body fluid loss might thus be brought about.

BURNS OF THE EYE

Patients treated at the Massachusetts General Hospital after the Cocoanut Grove fire had 5 per cent sulfathiazole and petrolatum placed in the burned eyes, the lids closed, and the eyes incorporated in the pressure dressing of the face, only the nostrils and mouth being left uncovered.

Jacoby (1942) said he had used the following treatment successfully in several hundred cases of shipyard workers who had sustained "flash" ultraviolet burns of the eye: instill one or two drops of 1 per cent pontocaine into each eye and have the patient sit before an infra-red lamp at a distance of approximately 18 inches and gaze steadily at the lamp for a period of twenty minutes.

For the treatment of chemical burns see below.

CHEMICAL BURNS

I believe it is the consensus that in cases of acid or alkali burns the heat of chemical reaction from neutralizing agents more often than not may add injury to that already produced by the caustic agent, and that therefore the best results are to be expected when the agent is flushed away through the copious use of water. However, the temptation to effect neutralization is so great that probably most acid burns are treated with a 3 to 5 per cent sodium bicarbonate solution and alkali burns with vinegar or a 3 per cent acetic acid solution. If these agents are used in the eye to attempt neutralization the pain induced may be so great that anesthesia should be instituted first. Poser and Haas (1943) proposed a phosphate buffer solution for the neutralization of both acid and alkali burns: 70 Gm. of monobasic potassium phosphate and 180 Gm. of dibasic sodium phosphate are dissolved in 850 cc. of water. The advantage claimed for this phosphate buffer solution is that it will effect prompt neutralization of the offending chemical without introducing the new complication of an alteration in the *p*H of the tissues; application to the normal eye was said merely to result in some conjunctival hyperemia which disappeared on the following day. Terry (1943) wrote that he had practically eliminated serious burns from a large caustic soda manufacturing plant through an arrangement by which the burned worker could immediately drench the affected area with 5 per cent solution of ammonium chloride; in cases in which there is such delay that destruction of the epidermis has taken place he has the part drenched with the ammonium chloride solution for ten or fifteen minutes and then with plain water or normal saline for one hour continuously, thereafter treating as for a heat burn. The eyes are irrigated for five minutes with the ammonium chloride solution and then for the rest of the hour with boric acid-saline solution.

Chronic acid burns require special treatment because this agent does not hydrolyze within the tissues and its action may persist for many days: after initial lavage, apply wet dressings of 5 per cent ammonium polysulfide for three days, followed by wet dressings of 5 to 10 per cent sodium citrate, sodium lactate, or sodium potassium tartrate for the purpose of stripping the chromium from the tissues, the latter dressing to be continued for a period of three to five days also.

In their experimental studies Keating and Travell (1943) found that 95 per cent alcohol was by far the most effective agent for removing phenol (carbolic acid) from the skin.

Magnesium burns, which are sometimes encountered in industry, are very

likely to form a slow healing ulcer. Morani (1944) said that since metallic magnesium interferes with normal cell physiology and causes interferences with normal repair processes, prompt removal of metallic magnesium by excision of burnt skin under local anesthesia is required for healing.

White phosphorus gives rise to severe burns because it ignites spontaneously in the air and even when embedded in the flesh will continue to burn as long as air can reach it. During War II the British Ministry of Health issued a memorandum (British Medical Journal, February 20, 1943) on the treatment of phosporus burns, which I present here in condensed form: (1) thoroughly flush and wash the affected area with sodium bicarbonate solution (roughly 2 tablespoonfuls of the powder to a pint of water) and pick off with forceps any obvious particles of phosphorus disclosed by examination *in the dark* (phosphorescence); (2) swab the affected area with 1 per cent solution of copper sulfate to coat any remaining phosphorus particles with a dark deposit of copper phosphide, and remove with forceps or gauze as much of this as is possible without damaging the tissues; (3) immerse the affected area in the bicarbonate of soda solution for a long period—*i.e.*, small burns one-half hour, large burns one to two hours—or if immersion is impossible keep it covered with sterile dressings repeatedly wetted with the bicarbonate solution; (4) finally, do not dress as for an ordinary burn until reexamination in the dark has revealed complete lack of phosphorescence.

SHOCK

PRIMARY SHOCK

(*Immediate or Neurogenic Shock; Vasovagal Syndrome*)

The fright of injury or of a harrowing experience may cause an individual to become very cold and to look very ghastly, but if his pulse and blood pressure are normal and he has received only a very minor injury, or none at all, it is safe to assume that he is suffering only from fright and will recover when he becomes warm and reassured. However, there is a very definite type of "primary" shock in which the patient may complain at first of being warm and nauseated but soon becomes cold and clammy with extreme pallor, a slow feeble pulse, and a blood pressure so low that it may not be measurable. The patient usually faints. This type of shock may result from the severe acute pain of sudden trauma or the dressing of a wound, or even in rare instances from the prolonged intolerable pain of renal or biliary colic, from the excessive manipulation of viscera at operation, or even from a severe emotional strain.

Therapy

The experiments of Phemister *et al.* (1944) indicated that hemoconcentration does not occur in primary shock, and it is universal experience that these patients recover in an hour or so if they are put at rest in a recumbent position, kept warm and given a sufficient dose of an analgesic to control their pain. However, the patient must be continually watched because he may after a time go into true "secondary" shock, and therefore if there has been much

loss of blood or if the tissues have been considerably traumatized, it is probably good routine practice to attempt to forestall secondary shock by instituting treatment for it at once (see below).

SECONDARY SHOCK

(Delayed, Traumatic, or Oligemic Shock)

This is the type of shock which occurs insidiously an hour or more after a patient has received a severe injury. As a result of massive hemorrhage either externally or into the tissues, or of the considerable loss of plasma externally in the burned patient or through extravasation into the tissues in the severely traumatized one, there is reduction in circulating blood volume, reduced cardiac output and diminished venous return. Usually the hematocrit reading and the hemoglobin percentage are well below normal as a result of the compensatory dilution of the blood with fluids from uninjured tissues; but at times hemoconcentration is recorded, particularly in severe burns and in instances in which there has been a great deal of plasma extravasation into the tissues or of serous or seropurulent exudate into a cavity. In the beginning the patient manifests a rather purposeless recklessness and breaks out into a cold clammy perspiration and becomes very thirsty. As the state progresses he becomes increasingly weak and cold and pallid and the lips, ear-lobes and finger tips may become grossly cyanosed. One of the most valuable diagnostic signs is a subnormal temperature, though of course at times complications may prevent this. For a considerable period the blood pressure may remain nearly normal as a result of compensatory arteriolar constriction in the skin and splanchnic areas, but the pulse is usually small, weak and rapid. Cope (1944) said that Grant had reported some cases among the air raid casualties in England in which the pulse rate remained slow and called attention to the fact that most of these patients were over fifty years of age; for the rate to remain slow in younger people is extremely unusual. What causes deterioration of the patient's condition beyond this point is not yet definitely known—*i.e.*, whether it is the pooling of blood in persistently dilated vessels in specific areas, or a general vasodilatation resulting from anoxemia of the tissues, or the mounting acidosis, or a hypothetical toxin formed in the tissues—but the result is a progressive and persistent fall in blood pressure and death if the state is not vigorously combated before the fall has become very great. In some instances the systolic pressure will remain approximately normal nearly to the end but failure of the circulation will be indicated by a high diastolic pressure; Cope (1944) wrote of a dying man whose systolic pressure was 135 while the diastolic pressure was 110.

The most important point with regard to secondary shock is that when the patient has sustained injuries sufficiently serious so that shock may be expected he must be treated at once, for to wait for a profound fall in blood pressure before instituting therapy may be to allow the patient to go into the state of "irreversible" shock from which no amount of treatment will retrieve him.

THERAPY

Control of Hemorrhage, Wounds and Fractures.—A few years ago, McMichael (1942) stressed the point, as a result of experience in the air raids in England, that the patient should be undressed as quickly as possible in order to make a full assessment of the extent of the injuries. Further blood loss should

then be stopped as quickly as possible by the application of compression band ages, digital pressure, hemostat, or ligature; a tourniquet should not be applied unless absolutely necessary since it so greatly interferes with the nutrition of the tissues beyond it. If, however, a tourniquet must be used it should be applied tightly enough to occlude both the arterial and the venous flows and it must be removed for a short interval at least every hour. The application of cold compresses or actual ice packs to the limb beyond the tourniquet may prolong the viability of the tissues. It is especially important to remember that when the tourniquet is removed permanently the return of the circulation to a badly damaged limb may result in a serious loss of plasma which can be prevented by the application of a compression dressing before the removal of the tourniquet. When the limb is so hopelessly damaged as to demand early amputation, the tourniquet should be left in place until the operation has been performed in order to prevent the loss of both blood and plasma. Extensive wound toilet should not be attempted as a first-aid measure; but if the wound is a penetrating one in the chest wall, it is imperative that the skin over it be closed by any means at hand. The urgent necessity to prevent any further damage to the soft tissues and the blood vessels makes it mandatory to attempt immobilization of fractures at the earliest possible moment, preferably before the casualty is moved from the scene of the accident.

Relief of Pain.—The relief of pain with morphine has been since time out of mind one of the primary principles in the treatment of traumatic shock, but it seems to me that there is nowadays rather good reason to question the sovereignty of the drug. For one thing, in shock the peripheral circulation is so sluggish that very frequently the patient doubtfully receives any benefit from the injected fluid because it is not absorbed; indeed Beecher (1944) reported that during War II morphine poisoning was encountered not infrequently in casualties who had been given several successive subcutaneous injections of morphine in the forward areas and then absorbed it all at a later time when they responded to the other measures directed toward the control of shock. Beecher advocated the administration of morphine intravenously in shock, or where that is not possible its deep intramuscular injection with following massage, the site of the injection being made low enough on an extremity so that if signs of poisoning subsequently develop a tourniquet can be placed above the morphine deposit in order to slow down the absorption rate. Then too, it is actually a fact that the patient in shock does not usually complain of pain, and therefore except for its quieting effect there would seem to be no reason for giving the drug; a quick-acting barbiturate, such as seconal or amytal, might often be effectively substituted, I should think. McMichael (1944) stated that during the blitz in England it was often observed that patients became restless and began to complain of pain only as the blood pressure was recovering; he felt that then was the time to give morphine, if necessary intravenously by injecting it into the infusion tubing. If there is severe head injury certainly the barbiturates only should be used for under these circumstances it is common knowledge that morphine greatly aggravates the state of anoxia; Gurdjian *et al.* (1939) made the further point that in these cases morphine produces a tremendous rise in cerebrospinal fluid pressure which may endanger the life of the patient.

Body Temperature.—The patient in shock both looks cold and feels cold and clammy to the touch, and therefore through the centuries we have been doing everything possible by the piling on of blankets and packing in of hot

bricks or water bottles to return him to a state of being warm to the touch and rosy in appearance; but it seems that everybody has been neglecting to determine whether we were not hastening his exitus in this way. The animal experiments of Blalock and Mason (1941), confirmed by those of Wakim and Gatch (1943), showed that significant elevations of temperature shorten the period of survival, a finding which need not be surprising in view of the fact that the cooler the tissues the lower their oxygen requirement. But it does not follow that the deliberate application of cold to the body of the shocked patient is therefore necessarily indicated, nor at the time of writing have I seen any report of a controlled series of cases in which the worth of such a procedure has been shown. The opinion of qualified clinical observers now seems to be, as I gather it from the writings of Cope (1944) and McMichael (1944), both summarizing extensive experience during War II in England, from the Harvey Lecture of Richards (1944) summarizing the studies of shock at Bellevue Hospital, from the memorandum on shock of the National Research Council of Canada (1943), and from our own National Research Council Military Manual on Shock and related conditions (1943), that sufficient covering should be applied to prevent great loss of body heat, but that the excessive and continued application of external heat should be avoided for three reasons: first, because warming of the skin will draw considerable blood away from the already depleted circulation of the vital organs; second, because the utilization of oxygen will thus be greatly increased; and third, because the patient may be caused to perspire which would only lead to a further depletion of his body fluid.

Position of the Body.—It is generally accepted that the head-low position, achieved by raising the foot of the bed 10 or 12 inches, is beneficial to the shocked patient, but one should remember the important exception, namely, that the patient with a head injury should have his head slightly elevated because when it is lowered there is likely to be an increase in hemorrhage both from the scalp wound and into the brain. Furthermore, rapid changes of position should not be made in any case; they may cause sudden death, just why is not known.

Restoration of Blood Volume.—In the present state of our knowledge this is undoubtedly the matter of foremost importance in the combating of shock; the several methods by which blood volume may be restored are therefore presented in comparative form below.

Dried Pooled Plasma.—This is the preparation with which most experience has been had for the reasons that: (*a*) it contains and retains without appreciable loss for many months all the various constituents of the previously liquid plasma; (*b*) it remains sterile under almost any conditions; (*c*) it survives a wider range of temperature variation than any of the other blood derivative preparations, though Newhouser and Lozner (1943) authcritatively stated that the package should not be allowed to freeze or be permitted to stand for any length of time above 55° C. (131° F.), and that if it has recently been stored above 37° C. (98° F.) it must be restored with water at not above 37° C. in order to avoid changes which may cause reactions; (*d*) the package can be opened, restored and prepared for administration in less than five minutes; (*e*) the reconstituted plasma need not be warmed to body temperature before giving; (*f*) it may be reconstituted in almost any amount of water desired.

With regard to the last point, it is the most usual practice to dissolve the standard unit of plasma obtained from 500 cc. of whole blood in the 250 cc. of sterile water which accompanies it in the package, the result being 250 cc.

of isotonic plasma; but one may easily prepare a twice concentrated plasma by simply using this 250 cc. of restored plasma as diluent for the dried plasma in another unit, and in this fashion even greater concentrations can be prepared.

As ordinarily employed in its isotonic form, *i.e.*, one unit of plasma reconstituted with 250 cc. of water, anywhere from 2 to 6 units, or 500 to 1500 cc., may be required to stabilize the blood volume. McMichael (1944), writing of extensive experience during the blitz in England, said that the transfusion may be given as quickly as the fluid will run into the veins up to the time that blood pressure has been restored and that thereafter it should be slowed to a drip, the drip being maintained till the end of any necessary operation. He furthermore pointed out that in previously hypertensive subjects the blood pressure will go on rising toward a higher figure than normal with quite moderate transfusion volumes and that in such patients the transfusions should be continued until a pressure of 140 to 150 mm. of mercury is reached.

Reconstituted plasma is administered by gravity from the container through a tube and filter, the injection usually being into the convenient basilic vein. However, in extreme shock the arm veins may be collapsed and one will be obliged to enter the femoral vein which is situated just medial to the femoral artery, the latter being readily palpable in the inguinal region; Dameshek (1944) pointed out that this route was found extremely useful in the Boston Cocoanut Grove disaster. Another route of entry, drawn attention to by Tocantins a few years ago, is the sternal marrow. The marrow cavity of the sternum is entered, under local anesthesia, by the introduction of a shortened stiff lumbar puncture needle through the skin and subcutaneous tissue and anterior lamella of the sternum until a sensation of give indicates that the needle has entered the marrow cavity; after withdrawing the stilet a small amount of marrow is aspirated before beginning the infusion. In children the marrow cavity of the tibia or femur is entered; Meola (1944) reported that his group had successfully given 326 infusions in this way to children.

It is the consensus that neither preliminary cross-matching nor skin testing are necessary before using plasma. The question of the likelihood of reactions of any kind occurring has been considered in two extensive reviews, one by Thalhimer (1942) of the Public Research Institute of New York City, and the other by Newhouser and Losner (1943) of the Naval Medical School; there was agreement that the dangers from *properly prepared pooled* human plasma are practically nil. The precautions under which plasma is collected for pooling preclude the possibility of the dissemination of syphilis in this way; Losner and Newhouser's (1943) study indicated that the likelihood of transmission of malaria by any plasma program, regardless of the type of preservation used, is also practically nonexistent.

Bruneau and Graham (1943) cautioned against the too liberal use of citrated blood because the citrate itself may be quite toxic, the reaction consisting in a general tingling sensation, dilatation of the pupils, and finally actual clonic twitching; such a reaction will be quickly terminated by the intravenous injection of calcium chloride or gluconate. The 250 cc. unit of plasma as customarily prepared contains 1.2 Gm. of citrate; since 15 Gm. of citrate given intravenously have been fatal, it follows that 6 units or 1500 cc. of pooled plasma bring one halfway to the possibly fatal dose of citrate and enjoin great caution in the further use of plasma, though admittedly the citrate reactions have occurred very rarely.

Liquid Plasma.—Liquid plasma is an excellent culture medium for bacteria

but when prepared by closed methods with scrupulously aseptic technic it may be preserved in the liquid state at room temperature in a temperate zone for at least as long as two years. Newhouser and Losner (1943) reported the administration of over 2000 doses of liquid plasma with a reaction rate of approximately 1 per cent; according to these authorities the permissible temperature range of preservation probably lies between 15° and 30° C. (59° and 86° F.). It is absolutely essential that a filter be used in the intravenous set when liquid plasma is administered because a small amount of fibrin precipitation is almost inevitable when plasma is preserved in this state. The chief advantage of pooled liquid plasma, as brought out by Dameshek (1944), is its ready availability, *i.e.*, the fact that it may be taken off the shelf and without further testing, reconstituting, or other steps, be given immediately to a patient in shock. It should be recognized, however, that during storage in a liquid state plasma rapidly loses complement and the antihemorrhagic factors, such as prothrombin.

Frozen Plasma.—When liquid plasma is frozen within twenty-four hours after preparation it may be preserved indefinitely if stored below −15° C. (5° F.) without loss of complement or prothrombin, and its sterility is preserved. However, thawing must be done in a water bath at 37° C. with occasional shaking and will require about thirty minutes. Plasma once thawed and then not needed immediately may be stored as liquid plasma or it may be refrozen; but in either instance much prothrombin and complement will have been lost. If accidental thawing has occurred the plasma may still be used, but in such a case a good filter must be employed because a certain amount of fibrin precipitation will have occurred during gradual thawing.

Liquid Serum.—Liquid serum may be stored at room temperature, but is probably preferably stored in a refrigerator, and is usable, under National Institute of Health regulations, until one year after preparation. Despite the absence of fibrinogen from serum its protein content is higher than that of liquid plasma because a diluent is added to the latter. Complement and antibodies are present in serum but prothrombin is absent. Numerous observers have expressed the opinion that plasma and serum may be considered clinically interchangeable substances so far as their employment in therapy is concerned, but serum has been upon the whole much more employed in England than in the United States.

Serum Albumin.—Human serum albumin has been separated from the complex plasma solution in relatively pure state and made available to the armed forces in a form which is quite stable at the moderate temperatures encountered in the temperate zones, though according to Newhouser and Losner (1943) it should not be stored at freezing temperatures or at temperatures exceeding 50° C. (122° F.). The standard Army-Navy package used in War II contained 25 Gm. of albumin in 100 cc. of buffered salt solution, and its administration was considered to be approximately equivalent to that of 500 cc. of citrated plasma so far as the ability to increase blood volume is concerned. However, Newhouser and Losner pointed out that its chief advantage is that it may be more easily stored where transportation space is at a premium. Its disadvantages are that it is extremely hypertonic and supplies practically none of the fluid that may be needed in the treatment of traumatic shock, burns, or hemorrhage; it may aggravate existing dehydration by pulling too much fluid into the blood stream; and it does not contain any of the antibodies or antihemorrhagic principles of plasma. Its production is also very expensive and it is therefore extremely unlikely to be much employed in civilian practice.

Bovine Albumin.—Dameshek's (1944) review indicated that the very interesting studies being made of this agent have not yet brought it to a point warranting a description of its use for practical purposes.

Whole Blood.—When whole blood has been lost in large amounts, as in severe hemorrhage or skeletal trauma, the restoration of blood volume by the use of plasma, serum, or albumin alone will produce an acute anemia and may actually limit the amount of these agents that can be safely given. The studies of the group at Bellevue Hospital, reported by Richards in his Harvey Lecture (1944), clearly brought this out as did also the experience with military casualties in War II. Though in many such instances one of the whole blood substitutes will be immediately life-saving, the transfusion of whole blood in substantial amounts as quickly thereafter as feasible is often required to combat serious degrees of anoxia.

Gelatin, Isinglass, Pectin and Acacia.—Each of these proposed substitutes for human plasma has had fairly extensive experimental and some clinical trial, but there are still relatively serious objections to the use of each of them which must be eliminated before it can be considered that they have acquired a definite place in the therapy of shock in the human. Acacia, which achieved some popularity after War I, has been practically discarded because it is deposited in the liver.

Physiologic Saline.—Since the introduction of plasma into the therapy of shock, there has been a tendency to dismiss intravenous saline infusion as of little value. However, it was found in the studies at Bellevue, reported by Richards (1944), that if given rapidly intravenous saline still merits a definite place in treatment as a temporary measure; while the blood volume in their cases, measured from one to three hours after the infusion of 1500 to 2000 cc. of saline, was increased by only 200 to 300 cc., the cardiac output was increased considerably and often restored to normal. A far more important use of saline, however, since blood or plasma is now generally available, is to combat dehydration which is sometimes a serious complicating factor in shock. A simple practical rule is that the patient is being maintained in a satisfactory state of hydration if an adequate urinary output is maintained. Du Bois (1942) pointed out that inasmuch as the amount of urinary pigment excreted in twenty-four hours is pretty constant from day to day, one can judge by the color of the urine the amount of solids that is being passed fairly accurately; therefore the amount of water which must be given by mouth, if the patient can take it, or of saline intravenously is that amount necessary to keep the urine light-colored. Where intravenous administration of saline is not feasible, not a great deal is to be expected from hypodermoclysis of saline in shock because of the poor peripheral circulation, but McMichael (1942) stated that large amounts of saline may be administered by deep intramuscular infusion into the lateral aspects of the thighs, the needles being pushed right down to the bone. In some instances it may seem advisable to add 5 per cent of dextrose to the saline if it is being given intravenously for the purpose both of supplying carbohydrate and combating acidosis, but the reader must be warned against the administration of excessive amounts of fluid of any kind by any route in shock because of the danger of precipitating pulmonary edema.

Oxygen.—In instances in which there is embarrassment of respiration due to traumatization of some portion of the respiratory apparatus, the administration of oxygen in high concentration is of course indicated. A great deal of study has been devoted to the question of oxygen administration in shock *per se*, both of hemorrhagic and traumatic origin. but I shall not review the

literature here since it does not show definitively that oxygen administration has a secure place in the therapy of these types of shock.

Drug Therapy.—It would be a mighty fine thing if we had a drug with which to combat shock, and the current researches which aim at the production of such an agent are certainly worthy of support; but as yet no satisfactory drug has been made available. Certainly all of the vasoconstricting agents are contraindicated because in shock there already exists a maximal reflex arteriolar contraction; epinephrine especially is not to be employed for the reason that its primary arteriolar constrictor action is succeeded by a prolonged generalized capillary dilatation. Ephedrine, benzedrine (amphetamine), metrazol, coramine (nikethamide), caffeine-sodium-benzoate, strychnine, and all the other analeptic agents have had their advocates but none has stood the test of time. During War II, Russian workers (Stern, 1942) claimed that the intracisternal injection of potassium phosphate proved its worth in the treatment of shock in the field, but a lot of evidence will have to be forthcoming to substantiate this claim.

CEREBRAL SHOCK

Sometimes in cases of severe head injury the circulatory disturbances will be neurogenic in origin in that they result from injury to the centers of cardiovascular control in the medulla—the blood pressure falls, the pulse becomes very slow oftentimes, and there may be deep, stertorous, or periodic breathing. In these cases the type of therapy employed in secondary shock not only fails to be beneficial but frequently aggravates the patient's condition because both the head-low position and transfusion tend to increase intracranial bleeding. I do not know what there is further to say about these cases except that the ministrations of a skilled, quick-working surgeon offer about the only hope that there is for such patients.

SURGICAL SHOCK

The shock which not infrequently occurs during a surgical operation differs from ordinary secondary shock in that in addition to the factors of the local loss of blood and plasma there is the insult of the anesthetic, the often prolonged emotional disturbance which preceded the operation, and the possible absorption of the toxic products of infection or autolysis. We do not have any magical procedures, however, which will combat all of these things, and the treatment of this type of shock must therefore in the present state of our knowledge remain that of secondary shock. Not infrequently recovery is spontaneous following the cessation of manipulation or the administration of the anesthetic. There is some evidence that animals with a low vitamin C level are more susceptible to shock than normal animals, and since the vitamin C level is said to diminish in the human after the performance of major surgical procedures, the suggestion has been made that the preoperative intravenous administration of vitamin C might be of value in preventing shock; I have seen no definitive clinical study in support of this suggestion.

CARDIOGENIC SHOCK

This is the type of shock which results from sudden diminution of cardiac output in myocardial infarction. There is neither decreased filling of the left ventricle nor loss of circulating blood volume and therefore the measures em-

ployed to combat secondary shock are not indicated here. This type of shock is more appropriately dealt with in Coronary Occlusion.

ANAPHYLACTIC SHOCK

In the literature of recent years there have been a number of reports of animal experiments in which there was recorded decreased blood volume and increased blood concentration in anaphylactic shock, these phenomena apparently resulting from a sudden wide increase in the size of the vascular bed consequent upon increased capillary permeability. In man, Black and Kemp (1937) observed an increase in the specific gravity of the blood during an acute reaction to ragweed pollen, and Meyler (1939) reported hemoconcentration in 2 cases of extensive serum disease in man. Blotner (1942) recorded the case of a patient in severe anaphylactic shock following the administration of tetanus antitoxin whose symptoms so closely resembled those of secondary shock that he treated him for the same, *i.e.*, he gave 2 liters of physiologic saline solution by intravenous infusion during two hours; it was considered that the response to this type of therapy was most satisfactory. Raynolds (1943) used plasma with equal satisfaction in his patient who developed anaphylactic shock following injection of pollen extract. These two case reports of course prove nothing, but they certainly do invite the interesting speculation that possibly the new type of plasma therapy for secondary shock might prove to be of specific value in the treatment of the oftentimes alarming anaphylactic shock.

CRUSH SYNDROME

This is an entity of which we have been made aware principally through the observations of the British during the blitz in War II. The patient is one in whom compression of muscle masses by heavy objects has been maintained for some time; after he is extricated from the wreckage and the compression is released he is likely to go into secondary shock in a few hours, and then in a matter of hours to days—oftentimes after the shock has responded well to therapeutic measures—evidences appear of progressive damage to the renal tubules. The true cause of this renal injury has not yet been determined but it is thought either to be due to some toxic product of damaged muscle tissue or to result from generalized intravascular hemolysis or to follow upon prolonged ischemia of the kidneys themselves. In fatal cases anuria develops and the patient is carried off in uremia usually a week to ten days after the injury was sustained. It seems that the extent rather than the duration of the concussion is of the greater importance in prognosis.

THERAPY

Under ordinary civilian conditions in peace time the therapy of this state will not vary fundamentally from that of secondary shock because in most instances the patient will have been released from the wreckage by the time the physician sees him. However, in the event that he is seen very early, at or shortly following his release from the wreckage, pressure bandages should be applied to the parts which have been involved and they should be only slowly released in order to prevent a sudden flooding of the circulation with the hypo-

thetical toxic products from tissue necrosis; the application of such pressure bandages will of course also prevent rapid extravasation of plasma into the damaged tissues and thus limit the degree of secondary shock. Plasma must of course be given, fresh liquid plasma without preservatives if possible, and fluids must be given by mouth and parenterally in the attempt to maintain a satisfactory urinary output. In the very complete discussion of the crush syndrome in publication 2212 of the Office of Civilian Defense (May, 1943), it was stated that 5 per cent dextrose solution is preferable for parenteral administration to saline solution because of the latter's edema-producing properties and its possible harmful effects on the damaged kidneys. The administration of alkalis to prevent the precipitation of myohemoglobin in the renal tubules has not been strikingly effective; the use of mercurial diuretics is absolutely contraindicated. Amputation of the involved extremity, decapsulation of the kidneys, multiple incisions into the tense, edematous, traumatized muscle masses, the administration of adrenal cortical substance and of atropine and papaverine, have all been tried but without consistently good results.

BLAST SYNDROME

This entity was seen a great deal during War II, especially during the blitz in England, but is unlikely to be observed often in peace time. Whether due to air or water (immersion) blast, this syndrome is associated with severe shock, often with injury to the central nervous system and the intra-abdominal viscera, and universally with lung damage. The predominant pulmonary lesions are bilateral and are due to hemorrhage and capillary bleeding following alveolar damage and rupture as a result of the impingement of a blast of air or water upon the body wall, pressure changes in the lungs transmitted through the trachea playing no part in the production of the lung lesions. Blast injury is sustained only by individuals who are within a few feet of the explosion and therefore in almost all instances the patient is suffering not only from blast but from severe injuries of the usual traumatic nature, so that the picture is nearly always a very complex one. Recovery from blast injury, when it occurs, is said to be apparently complete; Tunbridge (1945) listed deafness and post-concussive syndromes as the only sequelae.

THERAPY

According to the extensive discussion of the blast syndrome in Publication 2212 of the Office of Civilian Defense (May, 1943), the therapeutic dilemma in this entity is a very severe one, since both the shock and the pulmonary edema from which the patient is suffering require urgent attention. In the severe case with rapidly devoloping pulmonary edema venesection may be necessary as a life-saving measure, but since this is just the wrong thing to do for shock one must thereafter as soon as possible administer plasma intravenously. In some instances it seems that oxygen under positive pressure controls pulmonary edema without the resort to venesection. Since these injured lungs are extremely susceptible to the development of secondary pulmonary infection, the prophylactic administration of sulfadiazine might be advisable in selected cases.

TOXIC AND OTHER SPECIAL FEATURES OF SULFONAMIDE THERAPY

EXTENT OF OCCURRENCE OF TOXIC REACTIONS

With Full Dosage in Therapy.—The superiority of sulfadiazine to sulfathiazole for systemic employment against most infections is established upon the basis not only of greater efficacy but of lower toxicity. I shall not consume space with an extensive comparison of the toxicities of this whole group of agents since we all know that the use of sulfapyridine has been practically abandoned in the United States because of its high toxicity, particularly its penchant for causing violent vomiting, and also that sulfanilamide is very little used any more because of the relative limitation in its range of therapeutic activity; I am of course not concerning myself here with the local employment of sulfanilamide in surgical practice and in wound prophylaxis. Sulfaguanidine, formerly much used in the treatment of intestinal infections, has been shown to be much more freely absorbed and more toxic than was generally realized and has therefore been largely replaced by sulfasuxidine; the latter agent is very rarely absorbed to a sufficient extent to cause reactions. In a study of 900 sulfadiazine and 428 sulfamerazine-treated patients, Dowling *et al.* (1944) found toxic reactions occurring considerably more often in the sulfamerazine-treated series. It does not seem to me that enough experience has accumulated as yet with the newer drugs, sulfapyrazine and sulfamethazine, to enable one to make any categorical statements with regard to their toxicity in comparison with that of sulfadiazine, but since they have not yet been shown to be unequivocally superior to the latter drug perhaps this point is not of great importance.

It would therefore seem to be highly advantageous if we knew just about what to expect in the way of toxic reactions when sulfadiazine was administered in full dosage as in the treatment of a case of pneumonia for example. Fortunately, several such studies have recently been published, the most exhaustive being that of Plummer and Wheeler (1944), who recorded the occurrence of toxic reactions in 1357 patients to whom sulfadiazine was administered in therapeutic dosage. In this series of 1357 patients, 63 (4.6 per cent) experienced a renal reaction, in all but 5 instances unaccompanied by fever or rash; 22 (1.8 per cent) of the patients had a drug rash which was accompanied in 19 cases with fever; 15 of the patients (1.1 per cent) developed leukopenia with or without granulocytopenia; of the remaining 21 reactions, 4 were drug fever alone, 9 were nausea and vomiting, 1 was thrombocytopenic purpura (this was a fatal reaction), 2 were instances of jaundice, 1 of conjunctivitis, 1 of stomatitis, 1 of headache and vertigo, 1 of encephalopathy and 1 of arthralgia.

With Prophylactic Dosage.—Coburn (1944) reported that in the group of 30,000 Navy personnel to whom 15 grains (1 Gm.) of sulfadiazine were administered daily during three months, evanescent rashes occurred in 0.5 per cent of the individuals and dangerous constitutional disturbances in only 0.01

per cent. There was only one death in the series, that of a man to whom therapeutic doses of sulfonamides were given while he had a sulfonamide rash and bronchitis induced by the prophylactic employment of the drug.

LETHALITY OF THE TOXIC REACTIONS

In 1943, before sulfadiazine had come to be very much employed, Sutliff *et al.* made a study of sulfonamide toxicity as a cause of death in New York City, finding 28 such deaths reported during a year in which the total number of deaths in the city was 74,553. Analysis of their data enabled them to estimate that 1 sulfonamide death occurred for every 1610 pneumonia cases in which sulfonamide drugs were employed. One year later, in January, 1944, Osgood felt it still possible to regard with caution the early enthusiastic papers on low sulfadiazine toxicity which were then appearing and restated the facts regarding sulfonamide lethality as follows: (*a*) the death rate in better institutions for many of the commonly used sulfonamides is somewhere between 1 per 500 and 1 per 2000 patients treated; (*b*) this is far higher than the death rate from a general anesthetic with ether; and (*c*) it is considerably lower than the death rate to be expected when the precautions taken in such institutions are not observed. However, during that time Plummer and Wheeler were compiling their statistics on the use of sulfadiazine at the New York Hospital and were able to report, in their 1944 paper, that only one death had occurred in 2853 cases in which the drug had been used in therapeutic dosage either orally or intravenously. Thus we have in sulfadiazine a drug which is not only more effective but considerably less toxic than the earlier sulfonamides, but Osgood's observation is nevertheless still pertinent since the older figures on the lethality of ether averaged one death to about 16,000 anesthesias administered and doubtless a more modern compilation would show an even lower death rate than this. So the reader will do well to bear in mind that when he administers sulfadiazine to a hospitalized patient under ideal circumstances he is nevertheless subjecting him to a risk of death which is greater than when he has him anesthetized with ether under average conditions.

NATURE OF THE TOXIC REACTIONS

The various reactions will be discussed individually and in detail below, but in this place I wish merely to state that great progress has been made in recent years in the understanding of these lesions since performance of numerous autopsies on individuals who have died of sulfonamide poisoning has revealed the hitherto unsuspected fact that the sulfonamides can give rise to necrotic changes in the tissue cells. For example, in an individual dying of one of the frank and well-recognized types of reaction there may be revealed at autopsy focal necroses in the lungs, lymph nodes, spleen, adrenal glands, heart, blood vessels, etc. Furthermore, it is now known that a true toxic nephrosis is sometimes caused by these drugs as well as the more familiar type of disturbance resulting from precipitation of the relatively insoluble acetylated form of the sulfonamides. In brief summary then, one must say that although the sulfonamides are unquestionably among the most valuable agents ever

introduced into therapy they are nevertheless indubitably toxic and potentially dangerous drugs and should for that reason be administered with due respect for their harmful potentialities.

FACTORS INFLUENCING TOXIC REACTIONS

DOSAGE

Plummer and Wheeler (1944) were able to compare a group of 705 hospitalized patients given 6 Gm. of sulfadiazine daily with 115 hospitalized patients given only 3 Gm. daily; in the former group there were reactions of one sort or another in 9.2 per cent of cases whereas in the latter group there occurred only 1 reaction, a moderately severe drug fever, giving a percentage of 0.87. These workers also reported that in approximately 200 ambulatory patients given 3 Gm. of sulfadiazine daily for four days there occurred 1 case of mild granulocytopenia and 3 of mild renal irritation, each patient having had at least one urinalysis and two blood counts during the time of therapy; thus in this group there occurred reactions in 2 per cent of the patients. In addition there is the evidence of Coburn (1944) that only 0.5 per cent of evanescent rashes and 0.01 per cent of dangerous constitutional disturbances occurred during the administration of 15 grains (1 Gm.) of sulfadiazine daily for three months to 30,000 men. It is therefore very obvious that, except for the matter of sensitization which is to be discussed below, the higher the dosage the greater the likelihood of reactions. However, there is another matter to be taken into account and that is the total dosage of the drug and the length of time during which it is administered. In this latter connection, the extensive data of Plummer and Wheeler definitely did not suggest that the patient who has been receiving the drug for more than three or four weeks is safe from toxicity as has sometimes been stated; indeed they concluded that in an individual case the longer the drug is continued the greater is the chance of reaction in that case.

AGE

Several observers have stated the impression that infants and young children tolerate the sulfonamides better than adults, but to settle this question there would be required a study of reactions in an enormous number of individuals so that the numbers in the different age groups could be sufficiently comparable to permit accurate analysis. That this is true was evidenced in the study of Plummer and Wheeler, who had for example, 805 patients between the ages of twenty and sixty, 120 infants under one year of age and 82 children between the ages of one and five years—obviously no findings of statistical significance can be made on such disparate groups. However, there was an apparent decrease in the incidence of total toxicity in the infants in this series, which seemed to be accounted for by the low incidence of renal reactions, or perhaps one should say the low incidence of *recognized* renal reactions, in this group. It certainly does not seem to me that one is justified in administering sulfonamides with any less care to infants than to older individuals.

ROUTE OF ADMINISTRATION

Here again the most valuable study is that of Plummer and Wheeler, cited so frequently above. Of their 244 patients who were given one or more intra-

venous injections of sulfadiazine, 12.3 per cent had some form of reaction as compared with 8.9 per cent of reactions in 912 patients treated orally with 6 Gm. daily. The difference in the number of renal reactions in the two groups was even more striking; in those given intravenous injections renal reactions occurred in 7.4 per cent, whereas in those treated orally such reactions occurred in only 4.5 per cent. Furthermore, there were 2 cases of mild and transitory jaundice with possible toxic hepatitis which were thought to be probably attributable to the intravenous therapy since there were no such occurrences in the group of 912 cases given the drug orally. Decidedly, then, while the use of sodium sulfadiazine intravenously is a life-saving measure which must sometimes be resorted to, it must always be employed in the knowledge that in doing so one is considerably increasing the likelihood of the occurrence of serious reactions.

PREVIOUS ADMINISTRATION (*i.e.*, SENSITIZATION)

A very large proportion of our population has received or is now receiving one or the other of the sulfonamides by reason of falling into one of the following categories: (*a*) Persons who have received sulfonamides during a relatively brief period in the course of an illness in which their employment was definitely indicated. (*b*) Persons who have been given these drugs because it is the habit of their physician to prescribe them in practically all upper respiratory tract infections in the attempt to prevent complications such as sinusitis, otitis media, pneumonia, and so on. (*c*) Persons who have been given sulfonamides by urologists who were dealing with the problems of indwelling catheters or by general surgeons dealing with drainage tubes or employing the drugs prophylactically in the abdominal cavity. (*d*) Persons given sulfonamides in solution for local application to the nose and throat or in ointment form for the local treatment of skin lesions. (*e*) Persons self-administering sulfonamides when wounded on the battle-field or receiving sulfonamides while being treated for such wounds. (*f*) Soldiers on leave employing sulfonamides in the prophylaxis of gonorrhea. (*g*) Persons given the sulfonamides during the mass employment of these drugs in the armed forces in War II to check the dissemination of the hemolytic streptococcus and to prevent the occurrence of numerous entities of proved or presumed streptococcal origin. (*h*) Persons given these drugs in the attempt to prevent the recurrence of active symptoms after recovery from a bout of rheumatic fever. (*i*) Persons who have been given these drugs by the type of doctor (one likes to feel that the species is tending toward extinction) who routinely prescribes sulfonamides for all the ills to which the flesh is heir.

The question we face in connection with the employment of the sulfonamides upon the truly prodigious scale indicated in the above list of uses is a very simple one, namely, does the administration of a sulfonamide upon one occasion sensitize an individual to the drug so that if it is employed again after a lapse of time he is likely to react to it in a deleterious fashion, and if so, in what proportion of persons may we expect to encounter such sensitization and what can we do about it?

The facts regarding the occurrence of sensitization which have been so far established are the following: (*a*) The local cutaneous application of sulfonamides, particularly sulfathiazole, gives rise in a not inconsiderable proportion of cases when administration is continued for more than a week to a contact type of dermatitis, with or without a disseminate eruption, or a local

or generalized exacerbation of the skin disease for which the drug is being used. In some of these cases—I am unable to state the proportion because such figures are not yet available—the local sensitization thus induced persists so that when the drug is taken internally at a later time there will be a return of the local signs of sensitization. I have not seen any record of the occurrence of visceral lesions as a result of this cutaneous sensitization, but that is no reason to minimize the seriousness of this occurrence since the skin reactions as a result of sensitization may be very severe indeed and force the discontinuance of sulfonamide therapy when it is direly needed for the treatment of a serious systemic infection. Furthermore, some of these skin reactions have themselves resulted fatally. The studies of Shaffer *et al.* (1943) and others showed that in some instances the sensitizing application of the drug may not produce local dermatitis and can only be shown retrospectively to have sensitized the patient when he is seen to respond very quickly and in a violent fashion to a subsequent administration either locally or orally. (*b*) With regard to sensitization through the administration of a primary dose by mouth, the experience of numerous observers seems to establish with certainty a state of affairs comparable to the first type of cutaneous sensitization discussed above; namely, when an individual has received a sulfonamide for a week or more and has developed a reaction of some sort he is extremely likely to develop the same sort of reaction, but much more quickly and more violently, upon readministration of the drug after a lapse of time. In this connection witness the experience of Lee (1944), who recorded the administration for prophylactic purposes of a single 2 Gm. dose of sulfadiazine to 25,000 Army personnel; there were only 128 reported reactions of any sort and only 9 of these were considered to be "serious," but the important point is that 7 of the 9 occurred in patients who had previously experienced sulfonamide reactions. It is, however, not clearly established that a first course in which the patient develops no reaction may nevertheless sensitize him so that he will develop reactions upon subsequent administration. To be sure, Lyons and Balberor (1942) did report an experimental group of 53 patients, 36 per cent of whom developed a severe febrile reaction usually on the first day of a second course of sulfathiazole though none had experienced a febrile reaction upon the first administration of the drug, and that furthermore 8 of 10 of these patients had the same type of reaction upon the third administration. And similar isolated instances have been recorded, such as the single case reports of Nelson (1942) and Longcope (1943). But according to Leftwich (1944), the studies of Nelson upon a much larger series of patients did not bear out these findings; the latter author is said to have selected at random the records of 964 patients who had received sulfathiazole at the Johns Hopkins Hospital and to have found that the incidence of a febrile or cutaneous toxic reaction during the first administration of the drug to this group was 11.2 per cent, whereas upon second administration to patients who had shown no reaction to the first course of therapy the incidence was approximately the same, *i.e.*, 10.4 per cent in 133 patients. Using sulfadiazine, Plummer and Wheeler (1944) described toxic reactions in 11.5 per cent of 87 patients given a second course of the drug whereas they had observed such reactions in only 8 per cent of a much larger group of patients treated but once; however, the full value of this report is lost because it is not definitely stated how many of the patients who experienced reactions upon a second treatment had shown similar reactions upon the occasion of the first treatment. The report of Siegel (1944) probably indicated with

fair certainty that *short courses* of sulfadiazine may be frequently repeated without fear of the establishment of sensitization; *i.e.*, if one does not administer the drug long enough in any course to sensitize the patient there is apparently little to fear. The number of Siegel's children treated twice for recurring acute infections of the upper respiratory tract was 33, three times 23, four times 17, five times 9, six times 7, seven to sixteen times 10; treatment had to be interrupted in only 3 of the children because of an obvious intolerance to the drug, but the average duration of therapy in these cases was only four days.

There is much clinical evidence that hypersensitivity to the sulfonamides is a true allergic reaction whether it occurs upon the first or a subsequent administration of the drug, but as in other drug sensitivities patch or passive transfer skin tests have not been satisfactory as diagnostic aids. Leftwich (1944) reported extremely good results through skin testing a sensitivity suspect with the serum of another individual whose blood at the time contained a sulfonamide level of 2 mg. per 100 cc. or more; however, Jackson (1944) failed in what seemed to be a very thorough trial of this method. Randolph and Rawling (1945) studied the blood cellular reactions in 3 patients clinically sensitive: ingestion of a specific sulfonamide resulted in an initial diminution in total leukocytes and eosinophiles, a subsequent increase in leukocytes due in part to the presence of young myeloid cells, and, after the constitutional symptoms had subsided, return of the eosinophiles to or above the preingestion counts. As to duration of the hypersensitivity, there is the report of Erskine (1939), in whose patient 0.5 Gm. of sulfapyridine given twelve months after the original sensitization caused edema of the larynx; I have heard it stated that sensitization has been shown to persist for as long as three years but am unable to cite the records. It is probable, however, that most cases taper off in degree, for in a case of Dostrovski and Sagher (1944) the intensity of the fixed erythema reaction gradually was diminished during the course of ten months, and in the patient of Randolph and Rawling (1944) trial ingestion of the drug a year after the primary induction of a severe dermatitis, rhinitis and bronchial asthma resulted only in a diminution of the vital respiratory capacity.

As to prevention of sensitization, there can be no possibility of disagreement with the position taken by Livingood and Pillsbury (1943): (*a*) Since local sulfathiazole therapy is highly effective in acute frank superficial pyoderma but decidedly less effective in chronic exematous processes; (*b*) and since the prolonged use of the agent is extremely likely to be productive of reactions; therefore (*c*) such therapy should not be prolonged for periods of more than five days. One could doubtless set up with equal justification this five-day rule with regard to the local use of the sulfonamides on mucous membranes and their prophylactic employment in acute respiratory infections. In more serious infections in which relatively prolonged administration is necessary it has simply to be expected that sensitizations will occur and that they can be minimized only by reducing the period of sulfonamide administration as sharply as is possible under the circumstances.

It would seem that the pattern of treatment in patients who have exhibited a systemic toxic reaction was set by Lyons and Balberor (1942), who stated that in their series of patients who developed fever reactions upon readministration of sulfathiazole there were no instances in which sulfanilamide or sulfapyridine was not tolerated; at any rate the recent literature has not infre-

quently contained the statement that cross-sensitizations are unusual and that therefore a patient sensitive to one sulfonamide compound may usually be given another with safety. But this viewpoint is by no means in exact accord with actual experience. Plummer and Wheeler (1944) observed a variety of relationships between reactions and previous sulfonamide treatment. For example, one of their patients developed an acute febrile reaction after a test dose of each of the sulfonamides: sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine. In another patient, first sulfapyridine, then sulfathiazole and finally sulfadiazine produced a drug rash and fever. Their series of cases included only a few instances in which sulfadiazine was well tolerated by patients who had previously manifested toxic effects to sulfathiazole, but there were many examples of a similar type when sulfadiazine replaced sulfanilamide or sulfapyridine. The reverse of this, *i.e.*, tolerance to the other sulfonamides after intolerance to sulfadiazine, occurred very infrequently. As a result of their very careful study of the matter, Plummer and Wheeler have stated that no definite rules can be made for subsequent sulfonamide treatment in patients who have exhibited evidences of intolerance, except for the one rule that one must always be doubly cautious in such cases. They said that they have treated with great caution but successfully patients with past records of granulocytopenia, rashes and fever following the sulfonamides, and in most instances without repetition of the previous reactions; but they considered this practice to be a dangerous one which is to be avoided except in instances in which the necessity for reemployment of a sulfonamide is very urgent.

Park (1944) studied this matter very intensively in 40 sensitized patients. In 60 per cent of these individuals the allergy was confined to one sulfonamide drug but in the other 40 per cent included multiple sulfonamides and sulfanilic acid; furthermore, in about half of this multiply sensitive group there occurred reactions of sensitization to procaine also, though the latter is chemically related to the sulfonamides only by having a radical in common. In the matter of desensitization, Tate and Klorfajn (1944) found that the usual method of beginning with very small doses and increasing in the attempt to desensitize as in any other allergic state was ineffective, for as small a dose as 1/250 of a grain (0.25 mg.) given by mouth induced reappearance of the eruption. However, they did find that they could desensitize some of their worst cases by continuing sulfonamide administration in spite of further reactions in the skin, though the results were certainly severe and distressing for the patients; Dowling and Abernathy (1941) had a similar experience in the treatment of 4 cases of pneumonia with sulfapyridine. Nixon *et al.* (1943) did the same sort of thing in instances in which agranulocytosis appeared in severely ill pneumonia patients and in which the pneumonia was felt to be threatening the patient's life at least as much as the agranulocytosis; upon persistence with the employment of sulfadiazine, indeed even increasing the dose, they found that to their surprise granulocytes reappeared in the blood stream after a few days and the count steadily increased. It seems to me that surely one could be justified in resorting to this radical measure of continuing the employment of a sensitizing agent in the presence of a severe sensitization reaction only in cases of extreme emergency. How to understand the occurrences is certainly not explainable by me; someone has pointed out that iodism too may be overcome by continuing administration of the iodides, but I have never heard anyone suggest that iodism is an allergic phenomenon.

TREATMENT OF REACTIONS

Fever and Rash.—It is the consensus that at once upon the appearance of fever or a rash the administration of the drug should be stopped and fluids should be pushed in order to promote its elimination. What may be expected from shifting to another drug of the series, or indeed in instances of dire necessity pushing on with the offending drug itself, has been discussed under *Sensitization* above. Perhaps it should be mentioned, however, that there are some observers who feel that reactions in the skin which seem to be provoked only as the result of exposure to sunlight are in somewhat a class apart; at least Park and Platts (1942), studying reactions of this nature in the Middle East where they were seen with great frequency during War II, felt that in the milder cases at least these sunlight eruptions do not constitute an indication for discontinuing the drug. The local treatment is of course that indicated by the nature of the lesions (see the section on Skin Diseases). In Johnson's (1944) case of exfoliative dermatitis induced by the administration of sulfadiazine, the condition of the patient's skin seemed to resemble closely that following a severe scald, and he therefore treated him as for a burn: the skin was gently wiped with alcohol, sterile petrolatum strips were applied and overlaid with gauze packs and fluffs, and an elastic bandage was then wound snugly over all; the dressing completely covered the extremities and most of the torso and was left in place for nine days. Pain was controlled with morphine and supportive treatment included the administration of large amounts of fluid, dextrose, vitamins, plasma and whole blood. The patient recovered.

Hematopoietic Disturbances.—With sulfadiazine *hemolytic anemia* is extremely rarely seen (indeed it did not occur in a single instance in Plummer and Wheeler's, 1944, series of 1357 sulfadiazine-treated cases), but it followed the use of all of the older drugs of the series, particularly sulfanilamide. This anemia is of two types: one, a slowly developing hemolytic anemia in the course of which the patient's hemoglobin level drops 20 per cent or more in the first ten days of treatment, and another, which usually occurs in the first five days of treatment, which is a fulminating and very serious affair in which the hemoglobin may fall as much as 70 per cent in twenty-four hours and the erythrocyte count decrease, as in Gilligan and Kapnick's (1941) case, from 3,500,000 to 1,400,000 in twelve hours; other findings in these acute cases are macrocytosis, reticulocytosis, leukocytosis, an increased icterus index, urobilin in the urine, and in some cases hemoglobinemia and hemoglobinuria. The slowly developing cases of hemolytic anemia, which Long *et al.* (1940) found to occur in 3 per cent of their 1000 sulfanilamide-treated cases, are not considered alarming as they generally disappear when the drug is stopped and may be combated by the administration of 10 grains (0.65 Gm.) of ferrous sulfate daily; where it is desirable to continue sulfonamide administration, occasional transfusions should be given. In the acute cases, however, there is definite indication to discontinue the use of the drug at once and to alkalinize the urine, as suggested by Tragerman and Goto (1940), and subsequently recommended by Quick and Lord (1941), and Kracke (1944), in order to prevent deposition of the obstructing pigments in the renal tubules. If it is necessary to continue the administration of the sulfonamides in the presence of an acute hemolytic anemia, then heroic use of blood transfusions must be made in the attempt to replace blood as rapidly as it is destroyed. Dameshek (1943) thought the development of renal shutdown in some cases of acute hemolytic anemia is probably due to agglutination of red blood cells within the glomeruli

and subsequent blockage of renal tubules, since he and others found cold hemagglutinins present in the blood of some patients with severe hemolytic reactions. He also felt it well to remember that transfusions in cases of acute hemolytic anemia may be followed by severe reaction and that therefore as few transfusions as possible should be given.

During the course of treatment with apparently any of the principal sulfonamides an *acute leukopenia* with granulocytopenia may occur, particularly in children and usually during the first ten days of therapy. In many clinics the signal for stopping the drug and pushing fluids to promote its elimination is taken to be a fall in granulocytes below 50 per cent in adults and 40 per cent in children. True cases of *agranulocytosis* in which the typical blood picture is accompanied by angina are of much rarer occurrence; they have, however, been reported in association with the employment of all of the principal members of this series. This is a relatively late reaction, occurring in the experience of Long *et al.* (1940) after the fourteenth day of treatment and usually between the seventeeth and twenty-fifth days; Kracke (1944) did not postpone the time of occurrence quite so long but he said that at any rate the drug has usually been given from one to three weeks before agranulocytosis develops. Long *et al.* (1940) said the prognosis is good if the nature of the reaction is recognized at its inception and administration of the drug is stopped at once, but there are a number of deaths on record. For full treatment see the article on Agranulocytosis. Kracke (1944) said that the meager evidence at hand seems to indicate that if the patient has had agranulocytosis not only from a sulfonamide but from any other cause it is probable that a similar drug can be given again with safety.

Only a few cases of *thrombocytopenic purpura* have been reported but this is a serious reaction which may occur either early or late during treatment. The drug should of course be stopped at once and fluids pushed; for further discussion of this subject see the article on Purpura.

Very rarely a patient may manifest what Kracke (1944) called a *leukemoid reaction; i.e.*, there may be a marked leukocytosis, the total number of leukocytes reaching 50,000 or more per cubic millimeter, the granulocytes sometimes also showing a marked degree of immaturity.

Cyanosis appears in a very high proportion of patients treated with sulfanilamide, in far fewer treated with sulfapyridine, and very uncommonly in sulfathiazole- or sulfadiazine-treated patients. Most patients do not develop this sign until after considerable of the drug has been taken. The cause of the cyanosis remains unsettled, but Kracke (1944) felt it likely that an oxidation product actually stains the blood cells with the coincidental production of small amounts of methemoglobin. The condition is considered to have little significance, but Wendel (1939) said that the oral administration of $7\frac{1}{2}$ to 15 grains (0.5 to 1.0 Gm.) of methylene blue per day would prevent it; it has also been said that the use of nicotinic acid or the oxygen tent will do the same. Mackie (1939) warned that the taking of full doses of sulfanilamide just previous to flying would lower the aviator's "ceiling" by about 5000 feet, though Peterson *et al.* (1945), of the Canadian Army, concluded from the study of persons subjected to simulated altitude that sulfathiazole in full therapeutic dosage does not significantly alter the ability of normal individuals to withstand the effects of altitude and that use of the drug does not seem to be contraindicated for wounded personnel who are to be transported below 10,000 feet or above 10,000 feet with supplementary oxygen.

Hepatic Disturbances.—Hepatitis was observed by Long *et al.* (1940) in only 0.6 per cent of 1000 sulfanilamide-treated cases and it occurs even more rarely with the newer drugs of the series; for example, an occurrence described as "jaundice—possibly hepatitis" occurred in only 0.14 per cent of the 1357 sulfadiazine-treated patients of Plummer and Wheeler (1944). Menten and Andersch (1943), who studied the matter of hepatic damage in children, considered that it would appear desirable to determine the role of inadequate nutrition as a factor in the vulnerability of the liver to sulfonamides before finally evaluating the deleterious effects of these drugs upon the organs. The symptoms of such damage, according to Spring and Bernstein (1940), are anorexia, epigastric distress, nausea and at times vomiting, pain and tenderness in the right upper quadrant of the abdomen, jaundice, enlarged tender liver except in mild cases, hyperbilirubinemia, urobilinuria, biluria, and decreased hepatic function. Long (1940) made the practical point that jaundice with pale conjunctivae probably indicates that acute hemolytic anemia is developing whereas if the conjunctivae are not pale the jaundice probably results from liver damage.

Most of these cases of hepatitis fortunately clear up without sequelae if the drug administration is stopped at once and fluids are pushed; of course liberal carbohydrate administration is also indicated. But occasional cases have gone on to acute yellow atrophy and death. Many men feel that jaundice in itself contraindicates continuance of therapy with the sulfonamides, but the jaundice due to pneumonia was not so considered by Flippin *et al.* (1941) even before the days of sulfadiazine; hepatitis did not occur in any of their 400 cases, 200 of which were treated with sulfapyridine and 200 with sulfathiazole. Peterson *et al.* (1943) performed a careful study of the effects of the administration of sulfonamide compounds, particularly sulfathiazole and sulfadiazine, on the clinical course and hepatic function of 37 patients with various degrees of liver damage. They found: (*a*) that in patients with acute hepatitis associated with bacterial infections the sulfonamide therapy was almost invariably associated with improvement in hepatic function which paralleled the improvement in the underlying infection; (*b*) in patients with chronic damage to the liver hepatic dysfunction was not aggravated by administration of sulfathiazole or sulfadiazine and there was some improvement noted as a result of such therapy in cases in which bacterial infection was adding to the hepatic injury; (*c*) severe toxic effects of sulfonamide therapy other than direct injury to the liver were unusually frequent in patients with portal cirrhosis and were twice as common after sulfathiazole as after sulfadiazine.

Neuropsychiatric Disturbances.—It is now well known that the sulfonamides sometimes cause headaches, dizziness, visual disturbances, confusion, disorientation, and other behavior abnormalities, depression with lethargy and somnolence, or the opposite state of exaltation and even delirium. It is difficult to determine the absolute incidence of reactions of this nature but it is very evident that they are occurring much less frequently with sulfadiazine than with the earlier members of the series. Neither Reynolds and Shaffer (1943), nor Price and Pedulla (1944), were able to observe statistically valid changes in their attempt to make objective functional studies of these matters, but it nevertheless seems to me the part of wisdom for the physician to caution his patient to stay at home and rest while taking these drugs and not to make any important decisions or sign any papers during that time. Peripheral neuritis, myelitis and fatal encephalopathy have been reported, but such reactions

are of extremely rare occurrence. As a result of their experience in 9 cases of neuritis occurring in 1936 patients given full therapeutic sulfonamide dosage, Vilter and Blankenhorn (1944) stated that when this reaction occurs the necessity for continuing treatment must be weighed against the possibility of a persistent neuritis after recovery; it was not apparent in their series that thiamine, brewers yeast, or liver extract had preventive or curative value.

Renal Disturbances.—The sulfonamides are acetylated, probably principally in the liver, and the acetylated together with much of the remaining free form of the drugs is excreted in the urine. In the case of the newer agents developed since the introduction of sulfanilamide the acetylated forms are relatively insoluble in the urine and hence tend to appear there in crystalline form. Because they are irritating these crystals rather frequently cause microscopic hematuria and at times gross bleeding occurs. They may also collect in sufficient numbers somewhere along the tract—collecting tubules, renal pelves, ureters and bladder—to cause the obstructive type of anuria. With the exception of sulfanilamide, which has rarely caused any kidney disturbance, sulfadiazine is offending less in this respect than any of the other currently used sulfonamides, the reason being that if the urine is kept alkaline acetylsulfadiazine is the most soluble of any of the acetyl derivatives. For example, at this reaction (*p*H 7.5) acetylsulfathiazole reaches a solubility of only 28 mg. per 100 cc. whereas acetylsulfadiazine is soluble to the extent of 512 mg. per 100 cc. Sulfathiazole and sulfadiazine themselves are almost equally soluble in an alkaline urine (*i.e.*, *p*H 7.5) but—and this is the important point—acetylsulfathiazole is only four times as soluble in an alkaline as in an acid urine, whereas acetylsulfadiazine is more than twenty-five times as soluble under the same circumstances. The two outstanding facts here are the following: first, that urinary tract damage is certainly much less likely to occur with sulfadiazine than with sulfathiazole if the urine is kept alkaline, and second, that what is required is not just an arbitrary amount of alkali daily but the administration of sufficient in each case to maintain a urine definitely alkaline. Methods of accomplishing this are discussed in the articles on Pneumonia, Meningococcal Meningitis and Sepsis. Of course there should be an adequate fluid intake (3000 to 4000 cc. in adults) in order to maintain a urinary output of 1200 to 1500 cc. per day, but the reader should bear in mind that the attempt to prevent renal reactions by giving a high fluid intake has definite limitations as compared with alkalinization, since increasing the fluid intake twofold can only double the amount of acetylsulfadiazine dissolved whereas raising the urine from acid to alkaline in reaction will increase the solubility more than twenty-five times.

Arnett (1942) described a very practical method of keeping in touch with the status of the patient with regard to renal reactions by having the last urine passed exhibited at all times in a prominent place near the patient, *i.e.*, each time the patient voids, the old sample is discarded and the new one substituted. "The nurse sees it," said Arnett, "the intern sees it, and I see it (or if I do not I ask the reason why)." If the urine contains many sulfonamide crystals when it is first passed it looks muddy, but the crystals soon settle into a yellowish brown layer at the bottom of the container; orders are given that if the freshly passed urine appears muddy the fluid intake is to be increased or the sulfonamide dose decreased or both. If the urine appears bloody, the sulfonamide medication is stopped until further orders.

Urologists have sometimes found it possible to relieve sulfonamide anurias

by cystoscopically inserting catheters in the ureters and pelves and lavaging with warm physiologic saline or sterile water. Smith *et al.* (1940) brought about recovery in a case by resorting to bilateral pyelotomy, decapsulation and retrograde ureteral dilatation, and several reports of a resort to decapsulation have since appeared in the literature; Skibba (1944) resorted to the measure with success in an interesting case in which the anuria was due to the direct nephrotoxic action of the sulfonamides rather than to mechanical obstruction from precipitation of the acetylated compound.

In addition to the reactions resulting from the deposition of crystals, above discussed, there are now two other types of sulfonamide renal damage recognized. In the first of these, in which there may indeed be fatal anuria, the kidney is simply one of numerous organs involved in a widespread focal necrotic type of reaction. The second bears all the earmarks of an acute localized toxic attack. Murphy *et al.* (1944) studied 14 instances of this latter type of reaction, 13 of the 14 patients having died and been studied post mortem. All of the kidneys presented simple tubular degeneration regardless of what other changes were present; in some this process was advanced and there was necrosis of the tubular cells and intense inflammatory reaction outside the nephron in the surrounding tissues. In 1 case advanced changes in the glomeruli were observed. Of course there is nothing to say regarding therapy in these cases except to note that in the 1 patient of Murphy *et al.* who recovered decapsulation of the kidney had been performed.

Cardiovascular Reactions.—Sometimes at autopsy it has been observed that the myocardium has shared in the widespread focal necrotic type of reaction in which many other organs are also involved, but according to Grill (1944) clinical evidences of these myocardial reactions have not been seen except perhaps in the form of nodal arrhythmias detectable in the electrocardiogram. Comparable changes in the smaller blood vessels may however manifest themselves in nutritional disturbances and cause clinical symptoms similar to those of periarteritis nodosa. From the standpoint of therapy there is nothing to say about these things.

Arthralgia.—For the patient who develops arthralgia, *i.e.*, pain and perhaps stiffness in the joints but without heat, redness, or swelling, there seems nothing to do save stop the administration of the drug since the ordinary analgesic agents do not control this pain; however, Whitehouse and Bargen (1943) reported the case of a patient, being treated for colitis, in whom both sulfaguanidine and sulfasuxidine could be employed without reactions though sulfathiazole was invariably followed by an intolerable arthralgia.

Minor Toxic Reactions.—In Plummer and Wheeler's (1944) series of 705 patients who were given full sulfadiazine dosage orally for periods of two to fourteen days, none of them having received sulfonamide therapy of any sort previously, 92 per cent showed no recognizable toxic manifestations whatsoever and the much lower incidence of minor toxic effects following sulfadiazine as compared with sulfanilamide, sulfapyridine, or sulfathiazole was quite impressive. Nearly all patients are made "sick" by sulfapyridine; at best they have no appetite and appear gray and depressed and unhappy, and usually they are severely nauseated and vomiting. Sulfathiazole and sulfanilamide cause severe vomiting much less often than sulfapyridine but the patient taking one or other of these drugs is nevertheless frequently nauseated and depressed and complains of headache or other symptoms. Upon the other hand, the patient taking sulfadiazine usually makes very little complaint;

nausea or loss of appetite is rare, his color is normal and he is not depressed. There is very little to do for these minor reactions. In the days when sulfapyridine was still being much used, Brown *et al.* (1940) reported that nausea and vomiting could be materially lessened by suspending the powdered sulfapyridine in mucilage of tragacanth; the evidence regarding the value of the supplementary administration of nicotinic acid was conflicting and one hears nothing of it any more. It used to be stated that sulfanilamide caused acidosis, but I believe that the careful work of Hartmann (1939) disproved that contention.

SULFONAMIDE ANTIDOTES

It does not seem to me that there are any. The assertion has been made that ascorbic acid is of value, but Dowrie and Abramson (1944), who administered large doses of this vitamin orally to 25 children, did not find that it had any detoxifying effect upon either sulfathiazole or sulfadiazine. Detoxication by liver extract has been reported in experimental animals but I have not seen any convincing evidence of its value in man.

SULFONAMIDES AND DIET

During the early days of therapy with the drugs of this group, when it was thought that cyanosis was of serious import, severe dietary restrictions were made in order to reduce the amount of sulfur absorption and thus perhaps also limit the production of sulfhemoglobinemia. Now such restrictions are definitely outmoded because cyanosis has been put in its place as an unimportant reaction and because a *really* sulfur-poor dietary is a very difficult thing to provide anyway. So nowadays we feel that the patient on a sulfonamide drug may eat anything which is otherwise permissible in the disease for which he is being treated. But he should be forbidden to drink alcoholic liquors as they greatly increase the tendency toward, and the degree of, the psychotic reactions to the sulfonamides.

SULFONAMIDES AND OTHER DRUGS

There exists indubitable evidence in animal experimentation of the summation effect of the sulfonamides and the sedatives and general anesthetics. But I am unaware of any real substantiation of these findings in the human. Adriani and St. Romain (1942), who reported some of the positive findings in the lower animals, were obliged to report negative findings in man; at least the anesthesias proceeded quite normally in a series of 23 patients given cyclopropane, 25 ether and 5 pentothal, all the patients having received the usual premedication with morphine and scopolamine or atropine and some of them receiving in addition seconal, phenobarbital, or pentobarbital. Experience in War II has certainly amply shown that one does not need to fear the use of general anesthetics in patients who are taking full dosage of any of the sulfonamides. Quite another matter, however, is the finding that the sulfonamides may be inhibited by certain of the local anesthetics chemically related to para-aminobenzoic acid, which is itself the great sulfonamide inhibitor. Peterson and Finland *et al.* (1943) showed that procaine (novocaine) in amounts

ordinarily employed for local anesthesia may be absorbed into the circulation in sufficient concentration to exert a definite inhibiting effect on the action of sulfonamide drugs that may be present in the blood. It would therefore seem highly advisable to use local anesthetic drugs other than para-aminobenzoic acid derivatives for infiltration in extensive operative procedures on patients having severe infections in which rapid and effective action of the sulfonamide drugs is essential; furthermore, since infection introduced into an area which has been infiltrated with procaine may become established locally in spite of the continuous presence in the body of bacteriostatic concentrations of sulfonamides, it certainly seems desirable to use local anesthetics other than the para-aminobenzoic acid group when performing exploratory punctures of potentially infected areas. According to De Waal *et al.* (1942) the local anesthetics allied to para-aminobenzoic acid are procaine (novocaine), larocaine, tutocaine, butyn, anaesthesin and orthoform; those not so allied are cocaine, tropacocaine, eucaine (benzamine), stovaine, nupercaine, phenocaine, pantocaine, psicaine, eccaine, elypin, apothesine, diothane and metycaine.

Niblock (1941) observed 6 patients in whom the toxicity of the sulfonamides seemed to be increased through the simultaneous administration of quinine, and Harned and Cole (1942) found that at least in experimental animals sulfonamide absorption is indeed greatly increased through the action of quinine. I have seen no further reports of work of this nature.

The former fear of administering magnesium sulfate as a cathartic, or any other sulfur-containing compounds, has been dispelled as we have come to understand that sulfur absorption bears no relationship to sulfonamide toxicity.

PLACENTAL SULFONAMIDE PASSAGE

Sulfonamides administered to the pregnant woman are distributed in approximately the same concentration in the blood of the fetus as that attained in the blood of the mother; ready passage across the placenta therefore makes it possible to administer these drugs to the fetus by giving them to the mother. Speert (1943) found, however, that sulfonamides given to women in labor are poorly absorbed but that if they are given intravenously fairly comparable concentrations are quickly reached in the fetal and maternal bloods. Speert suggested the employment of sulfonamides therefore in cases of prolonged labor with ruptured membranes in order to prevent bacterial invasion of the fetal vessels and also to protect the fetus against intra-partum infection in cases in which gonococcal infection of the mother is suspected. It would be desirable, it seems to me, if there were available sufficient evidence from which to form an opinion regarding the toxic effect in the fetus and the newborn as the result of sulfonamide administration to women during pregnancy and labor. Heckel (1941) reported 13 mothers taking a sulfonamide, and in 1 case the baby suffered from severe anemia and jaundice which it was felt might possibly have been due to the treatment; Ginzler and Chesner (1942) also reported 2 cases in which the fetus seemed almost certainly to have been deleteriously affected by the drug administered to the mother. However, this is a small number of cases upon which to base an opinion and it would certainly seem desirable for someone to undertake a well-planned large-scale study of this subject.

SULFONAMIDE CONTRAINDICATIONS

It is now the consensus that previously existing *jaundice* or other evidences of liver damage, or the presence of *anemia* or *leukopenia* before therapy is commenced, do not contraindicate the use of the sulfonamides within the limitations stated in the discussion of the toxicity of these agents. In the presence of severe *cardiac arrhythmias*, and especially of *congestive heart failure*, these drugs should be used with utmost caution; one had perhaps best be cautious in the use of these drugs in *coronary disease* also, for I have heard of instances in which their use increased the substernal distress. If there is *impaired kidney function* one should use sulfonamides with the greatest of caution; Allen (1940) suggested that under these circumstances the excessive acetylation of the drugs may increase their toxicity. If an individual has had a severe sulfonamide reaction and subsequent employment of the sulfonamides is imperatively indicated one must proceed with utmost caution; Long (1940) said that if nothing has happened during a twelve-hour period following the administration of a small test dose of 2½ to 5 grains (0.15 to 0.3 Gm.), treatment may be begun but must be pursued throughout with especial watchfulness. When sulfanilamide was the principally employed agent of this group there appeared several reports indicating the possibility that the employment of *roentgen ray therapy* concomitantly with the administration of the drug increased the likelihood of severe reactions particularly of a hematopoietic nature. However, there have been no publications on the subject since sulfadiazine has so largely replaced the other members of the series, and I do not know any radiologists who fear the situation at all. It should be stated here, however, that an unknown author, answering a query in the Journal of the American Medical Association in the middle of 1942, categorically stated that roentgen therapy is not to be employed when the sulfonamides are being used.

MINIMAL PRECAUTIONS WHEN ADMINISTERING SULFONAMIDES

The renal reactions are the most to be feared since they occur with the greatest frequency and are often very serious; a simple method by which the practitioner may keep himself fully informed with regard to the state of affairs in this respect in a patient being treated by the sulfonamides in his home is described in the section on the renal reactions to these drugs. It is of course assumed that proper dosage, with proper alkali coverage, will be given to the patient. Then there is the matter of the blood reactions. Acute hemolytic anemia, which is seen much less frequently since sulfanilamide is not very much employed any more, will usually be recognized by the alert physician who is on the lookout for the symptoms discussed in the section on the hematopoietic reactions to these drugs. Agranulocytosis is usually a late occurrence and purpura, though it may occur either early or late in the course of treatment, a very rare one. Therefore it would seem that the physician is justified under ordinary circumstances—proper dosage, proper alkali coverage, proper fluid administration, the indicated precautions against unobserved renal damage, alert and thoughtful observation of the patient—in proceeding with the administration of the sulfonamides in the home for a week to ten days without blood examination; thereafter it would seem advisable that not only red and

white counts be made twice weekly but that differential counts be made also. And routine examination of the blood one month after therapy has ceased might also be in order, since Bigg and Harvey (1941) reported a case and cited a number of others in which serious reactions occurred as long as three weeks after cessation of therapy.

SULFONAMIDE RESISTANCE OR "FASTNESS"

Most clinicians of wide experience have found that in a few instances switching a patient from one to another of the sulfonamides will be effective in cases of sulfonamide resistance, but in the vast majority of instances an organism resistant to one sulfonamide seems to be resistant to them all. Fortunately sulfonamide resistance does not imply penicillin resistance, nor, when local therapy is concerned, resistance to gramicidin or propamidine.

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